Respiratory Tract System

(RESPIRATORY DISORDERS)

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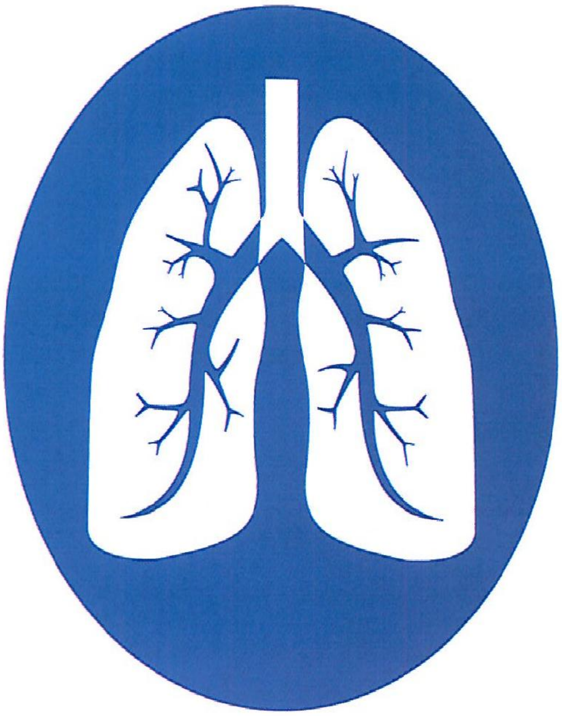
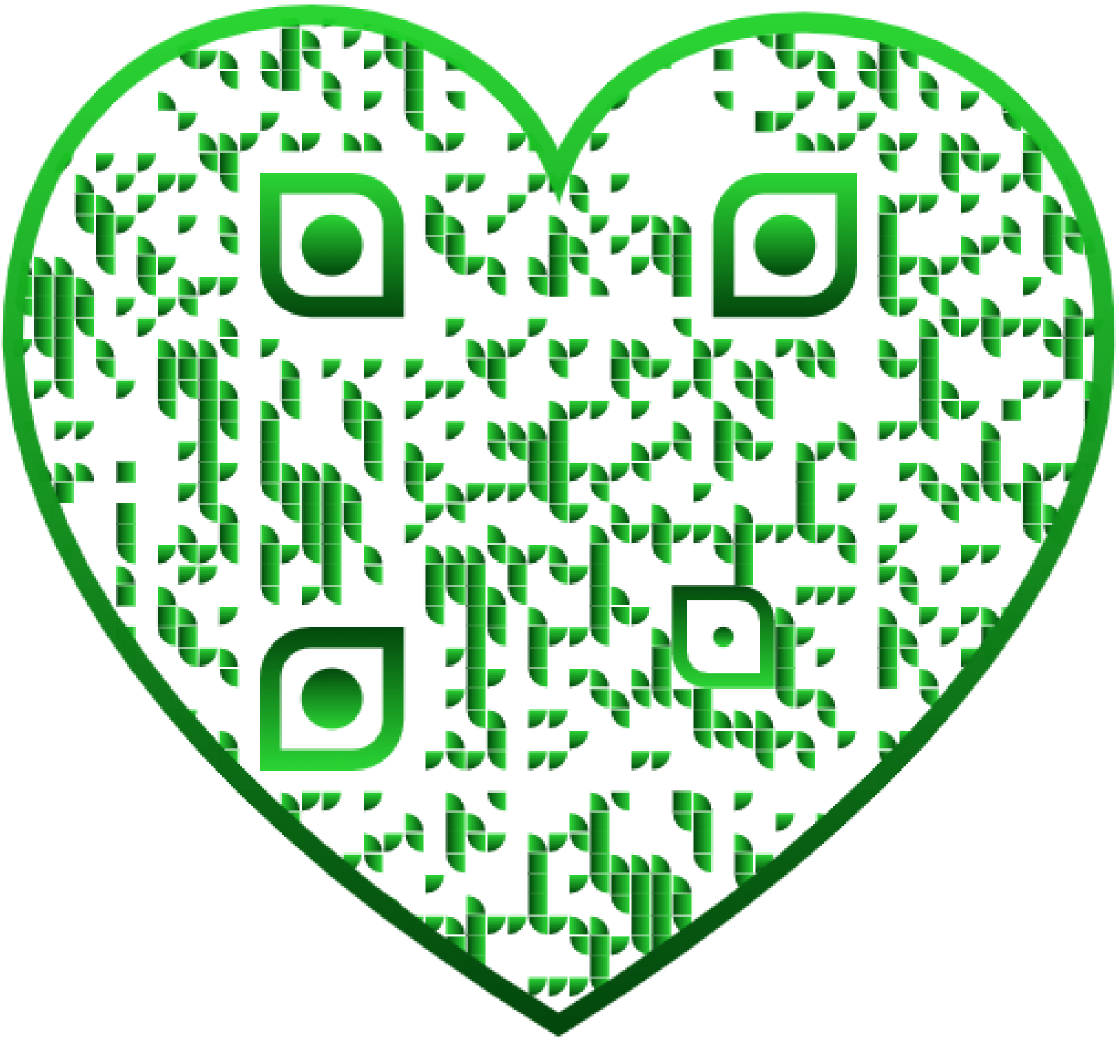
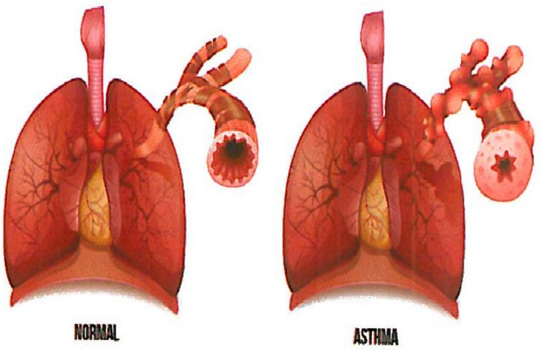
Respiratory Tract Infections (RTIs) are discussed in infectious diseases in chemotherapy chapter





Asthma

➢ Overview:-



- **Asthma** is a ***common chronic*** **inflammatory disease** of the ***airways*** of the **lungs**.
- It is the ***most common*** **chronic disease** in **childhood**.
- The **pathophysiology** of **asthma** is ***complex*** and ***involves*** **airway inflammation, intermittent airflow obstruction, & bronchial hyperresponsiveness**.
- It is **characterized by** ***variable*** and ***recurring*** **symptoms**, ***reversible*** **airflow obstruction** and **bronchospasm**.
- **Asthma** is thought to be ***caused by*** a ***combination*** of **genetic** and **environmental factors**.
- **Chronic Obstructive Pulmonary Disease** (**COPD**); is a ***type*** of **obstructive lung disease** *characterized by* ***long-term*** **poor airflow**. The ***main symptoms*** include ***shortness*** of **breath** and **cough** ***with*** **sputum production**.

➢ Definition:-

- **Asthma**; is a ***chronic inflammatory disorder*** of the **airways** *causing* ***recurrent*** **episodes** *of*; **wheezing**, **breathlessness**, **cough** and **chest tightness**, *particularly* at **night** or ***early*** in the **morning**. ***During episodes***, there is ***variable*** **airway** ***obstruction***, *often* ***reversible*** **spontaneously** or ***with*** **treatment**. *There is also* ***increased*** **bronchial hyperresponsiveness** to a *variety* of **stimuli** (exaggerated response to numerous exogenous and endogenous stimuli).

➢ Prevalence:-

- **Asthma** is a ***common*** **chronic disease worldwide**.
- **The Global Asthma Report 2014**; *approximately* **234 million** ***people worldwide***.
- **Rates** ***vary*** *between* **countries** *with* ***prevalences*** *between* **1** and **18%**.
- *Approximately* **23 million** ***persons*** are *affected by* **asthma** in the **United States**.
- It is the ***most common*** **chronic disease** in **childhood**, affecting an estimated **7 million** ***children*** in the **United States**.

➢ Pathophysiology:-

- The ***pathophysiology*** of **asthma** is ***complex*** and *involves* the ***following*** **components**:
  - **Airway inflammation**.
  - **Intermittent airflow obstruction**.
  - **Bronchial hyperresponsiveness** (**BHR**).

Airway Inflammation

- The ***mechanism of inflammation*** in **asthma** may be; **acute**, **sub-acute** or **chronic**.
- ***During inflammation***; *varying* ***changes*** in the **airways** *includes* **eosinophil** ***infiltration***, **mucus** ***hypersecretion***, **epithelial cell** ***desquamation***, **smooth muscle** ***hyperplasia*** and **airway** ***remodeling***.
- **Mast cells**, **eosinophils**, **epithelial cells**, **macrophages** and **T lymphocytes**; ***play*** an **important role** in the ***regulation of*** **airway inflammation** *through* ***release*** of **cytokines**.
- **Chronic inflammation** is *associated with* ***increased*** **bronchial hyperresponsiveness**, which *leads to* **bronchospasm** and **coughing** *after* ***exposure*** to **allergens**, **environmental irritants**, **viruses**, **cold air** or **exercise**.
- **Nervous system in the lung**;
  1) **Sympathetic Nervous System**.
  2) **Parasympathetic Nervous System**.
  3) **Non-Adrenergic Non-Cholinergic (NANC) Nervous System**.

Home Management

Acute Asthma Exacerbations

Inhaled SABA: up to 2 treatments 20 minutes apart of 2–6 puffs

Good Response

- No wheezing or dyspnea.
- May continue inhaled SABA every 3–4 hours for 24–48 hours.
- Consider short course of oral systemic corticosteroids.

Incomplete Response

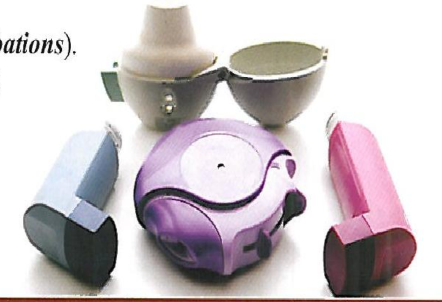
- Persistent wheezing & dyspnea.
- Add oral systemic corticosteroid.
- Continue inhaled SABA.
- Contact clinician urgently (this day) for further instruction.

Poor response

- Marked wheezing and dyspnea.
- Add oral systemic corticosteroid.
- Repeat inhaled SABA.
- If no response; **call your doctor immediately**.

Pharmacological Therapy

- **Asthma medications** are *generally* ***divided into*** **two categories**:
  1) **Quick relief** (**reliever medications**); *relieve acute asthma exacerbations*;
     - **Short-acting β2-agonists** (**SABAs**).
     - **Systemic** (**Oral**) **Corticosteroids**.
     - **Anticholinergics** (***only for severe exacerbations***).
  2) **Long-term control** (**controller medications**);
     - **Inhaled Corticosteroids**.
     - **Long-acting β2-agonists** (**LABAs**).
     - **Long-acting Anticholinergics**.
     - **Methylxanthines**.
     - **Leukotriene Modifiers**.
     - **Mast Cell Stabilizers**.



β2-adrenoceptor Agonists

- The ***β2-agonists*** are the ***most effective*** **bronchodilators** ***available***.
- ***In general*** ***activation*** of **β2-adrenergic receptors** ☞
  - **Smooth muscles**; **bronchodilatation** and **uterine muscle** ***relaxation***.
  - **Skeletal muscles**; **vasodilatation** and **tremors**.
  - **Heart**; **heart muscle** ***contraction***.
  - **Mast cells**; ***inhibition*** of **mast cell** ***degranulation***.
  - **Metabolic**; **glycogenolysis**, **gluconeogenesis**, **lipolysis**, **hypokalemia** and ***increase*** **lactate**.
- ***Side Effects***; **Tremor**, **Tachycardia**, **Hypokalemia**, **Hypomagnesemia** and **Hyperglycemia**.

Short-acting β2-adrenoceptor Agonists (SABA); Acute Asthma

Salbutamol or **Albuterol** (Ventolin®)	**Levosalbutamol** or **Levalbuterol** (Xopenex®)
Terbutaline (Bricanyl®)	**Pirbuterol** (Maxair ®)

- **Salbutamol** or **Albuterol** is the ***most commonly*** used **bronchodilator** that is ***available*** in **multiple forms** (e.g.; solution for nebulization, metered-dose inhaler, and oral solution).
  - *Dose*; - ***Metered-dose inhaler*** (***MDI***); 2 puffs every 4 to 6 hours as needed.
    - ***Inhalation capsules***; 200 mcg inhaled every 4 to 6 hours (may increase to 400 mcg inhaled every 4 to 6 hours, if necessary).
    - ***Nebulizer***; 1.25–5 mg in 3 cc of saline every 4 to 8 hours as needed.
    - **Tablet** and **syrup**; 2-4 mg orally every 6-8 hours (not to exceed 32 mg/day).
- **Levosalbutamol** or **Levalbuterol** is the ***R*-enantiomer** of **Salbutamol** or **Albuterol**.
  - *Dose*; - ***Metered-dose inhaler*** (***MDI***); 2 puffs every 4 to 6 hours as needed.
    - ***Nebulizer***. 0.63-1.25 mg in 3 cc of saline 3 times daily as needed.

Long-acting β_2-adrenoceptor Agonists (LABA); Chronic Asthma

- **LABA** *should not* use *for* **acute asthma**.
- **LABA** *used for* **prevention** (such as; **nocturnal asthma** or **exercise-induced asthma**).
- **LABA** *must be used in* **chronic asthma** in *combination with another long-term asthma-control medicine* (e.g. **Inhaled Corticosteroids (ICS)** such as **fluticasone** and **budesonide**); to *prevent* **ASTHMA-RELATED DEATH**.
- **LABA** in **COPD**; *may be* used as **mono-therapy** *or* in **combination** with **Corticosteroids.**

Formoterol (Foradil®) | Salmeterol (Serevent®)

- **Formoterol** and **Salmeterol** *duration of action* may extended up to **12 hours**.
- *Dose*; 1 puff or 1 inhalation capsule 2 times daily.
- **β_2-Agonist/Inhaled Corticosteroid Combinations**;

Product	Corticosteroid	β_2-Agonist
Symbicort®	Budesonide	Formoterol
Dulera®	Mometasone	Formoterol
Fostair®	Beclomethasone	Formoterol
Advair®- Seretide®	Fluticasone	Salmeterol
Breo® Ellipta®	Fluticasone	Vilanterol

- **Vilanterol** [vye-LAN-ter-ol] an **ultra-long-acting β_2 agonist (ultra-LABA)**, it was *approved by* **FDA in 2013** for **COPD**. In **2015**, *approved* **once-daily treatment** *for* **asthma** in **people ≥ 18 years**. **Breo® Ellipta** *contraindicated* in *patients with* **severe milk protein allergy**.
- **Indacaterol** [IN-da-KA-ter-ol] is the *first* **ultra-LABA**, **approved** *only* for **long-term control** of **COPD** *symptoms* (*not used* in **chronic asthma**).

Corticosteroids

- *Benefits* of *corticosteroids* in **asthma**;
  1) *Increasing* **number** and **sensitivity** of **β_2 receptors**.
  2) *Reducing* **mucus** *production* and **hypersecretion**.
  3) *Reducing* **airway edema** and **exudation**.
  4) *Reducing* **bronchial hyperresponsiveness** (BHR).
- *Mechanisms* of *corticosteroids* in **asthma**;
  - *Suppress* **several proinflammatory cytokines** → *reducing* **inflammatory cell** *activation* and *infiltration* → *decreasing* **vascular permeability**.
  - **Reducing** *production* of **leukotrienes** by *inhibiting* **phospholipase A2**.
  - *Prevent* **action** of **proinflammatory cytokines** *on the* **cell**.
  - *Increase* **β_2 Receptor density** (within 4 hours of corticosteroid administration) and *improve* **responsiveness** of **β_2-agonists** (within 2 hours of corticosteroid administration).
  - *Reversal increased* **BHR** (requires at least 1 week of therapy).
- *Side Effects* of **Chronic Systemic Glucocorticoid Administration**;
  - Hypothalamic–pituitary-adrenal suppression
  - Skeletal muscle myopathy
  - Aseptic necrosis of bone
  - Pseudotumor cerebri
  - Sodium and water retention
  - Hypertension
  - Impaired wound healing
  - Posterior subcapsular cataracts
  - Central redistribution of fat
  - Growth retardation
  - Osteoporosis/fractures
  - Pancreatitis
  - Psychiatric disturbances
  - Hypokalemia/hyperglycemia
  - Skin striae
  - Inhibition of leukocyte and monocyte function
  - Glaucoma
  - Moon facies

Oral (Systemic) Corticosteroids; Acute Asthma

Prednisone (Hostacortin®) | Prednisolone (Hostacortin-H®)

Methylprednisolone (Solu-Medrol®)

- **Prednisone** is a ***prodrug*** which ***converted*** via *liver metabolism* to **Prednisolone** (active).
- **Oral Corticosteroids** are ***used for*** **short courses** (3-10 days) to control **acute asthmatic episodes.**
- *Dose*; 40–80 mg in 1 or 2 divided doses.
- ***Administration*** of **systemic corticosteroids** (oral and parenteral are equally effective) ***within*** **one hour** of **emergency department** in **acute asthma exacerbation** → ***decreases need for*** **hospitalization.**

Inhaled Corticosteroids (ICSs); Chronic Asthma

Beclomethasone (QVAR®)	**Fluticasone** (Flovent®) (Flixotide®)
Mometasone (Asmanex®)	**Budesonide** (Pulmicort® Flexhaler) (Miflonide®)
Triamcinolone (Azmacort®)	**Flunisolide** (Aerospan®)

- **ICS** are the ***first line*** (*drugs of choice*) for ***long-term control any degree*** of **persistent asthma.**
- **ICS** are given as *long-term* to *avoid* **adrenal insufficiency**, ***but*** **high doses of ICS** *may cause* **adrenal suppression.**
- *Onset of improvement*; **5–7 days** (additional benefit may occur over several weeks).
- **ICS** *have few systemic* **side effects** (consider **Calcium** and **Vitamin D** ***supplements*** in **adults**, particularly in premenopausal women).
- **ICS** *local* **side effects**; due to ICS deposition on the **oral** and **laryngeal mucosa** can cause;
  1) **Oropharyngeal candidiasis (Thrush)**; due to local immune suppression.
  2) **Hoarseness (Dysphonia)**; due to myopathy of the vocal cords.

  *** **Patients** ***should be*** **gargle water** and **spit** ***after*** *each* **inhaled treatment** to ***decrease*** the **chance** of these ***local*** **adverse events.**

Ciclesonide (Alvesco®)

- **Ciclesonide** [sye-KLES-oh-nide] is ***recently approved*** **ICS** as a **prodrug** ***activated by*** **esterases** in **lung** to *form* **its active metabolite** (**Desciclesonide**)
- ***Because*** it is ***not activated*** **until** it ***reaches*** the **lung**, **Ciclesonide** *may cause* ***fewer*** **local side effects.**
- **Desciclesonide** is ***tightly*** **bound** to **plasma proteins**, and so has ***little*** **access** to **glucocorticoid receptors** in **skin, eye and bone,** ***minimizing*** its **risk** of ***causing systemic*** **side effects.**

Anticholinergics

- A ***number*** of the **triggers** and **mediators** of **asthma** (i.e., **Histamine**, **Prostaglandins**, **Sulfur dioxide**, **Exercise** and **Allergens**) ***produce*** **bronchoconstriction** in part ***through*** **vagal reflex mechanisms** (parasympathetic stimulation).
- The **anticholinergic agents** ***block*** **vagally** *mediated* ***contraction*** of **airway smooth muscle** and **mucus secretion.**
- *Side effects*; **Headache, flushed skin, blurred vision** and **tachycardia.**

Ipratropium (Atrovent®)

- **Ipratropium** [IP-ra-TROE-pee-um] is a ***non-selective*** **muscarinic receptor blocker**, **quaternary ammonium derivatives** (*not cross BBB*).
- *Indications*;

  Off-label; 1) ***Acute*** **severe asthma** in **patients** ***not completely*** **responsive** to **β_2-agonists** ***alone.***

  Approved; 2) **Chronic Obstructive Pulmonary Disease (COPD).**
- *Onset of action*; **30–60 minutes (β_2-agonists; 5–10 minutes).** - *Duration of action*; **4-8 hours.**
- ***Dose for Acute*** **severe asthma** (**emergency**); ***Off-label***
  - **Metered-dose inhaler** (*MDI*); 8 puffs every 20 min as needed for up to 3 h.
  - **Nebulizer**; 500 mcg (1 unit dose vial) every 30 min for 3 doses, then every 2–4 h as needed.
- *Anticholinergic agent combinations*; **Ipratropium** + **Salbutamol** (Combivent®) (DuoNeb®)
- A ***longer-acting*** **antimuscarinic agent** such as **Tiotropium** and **Aclidinium**; are ***approved*** and ***used only*** in **COPD** (*not used* in asthma), ***but*** ***recently*** **Tiotropium studies well** in **chronic asthma** and is ***approved***; **Spiriva® Respimat** ***only.***

Tiotropium (Spiriva® Respimat)

- **Tiotropium** [TYE-oh-TROE-pee-um] is a ***selective*** **muscarinic receptor blocker** (***mainly on*** M_3), used in ***management*** of **COPD.**
- ***Recently*** **Tiotropium studies well** in **chronic asthma** and is ***approved***; **Spiriva® Respimat** [inhaled spray] ***only*** is used in **chronic asthma**;
  - **Spiriva® HandiHaler** [inhaled capsule] ***used*** in **COPD** but ***NOT used in*** **chronic asthma.**
- ***Dose for*** **chronic asthma** (**Spiriva® Respimat**); **2 puffs** ***once*** **daily.**

IV magnesium sulfate increases lung function and decreases hospitalizations in children with an acute asthma exacerbation

Methylxanthines

- The **3** ***important*** **methylxanthines** are **Theophylline**, **Theobromine** and **Caffeine**.
- Their ***major source*** is **beverages (tea, cocoa,** and **coffee)**.
- The ***importance*** of **Theophylline** as a ***therapeutic agent*** in the ***treatment*** of **asthma** and **COPD**.
- **Aminophylline** is a **Theophylline** ***complex with*** **Ethylenediamine** is ***less potent*** and ***shorter-acting***. **Aminophylline** is the ***preferred*** **injectable product** owing to ***increased*** **solubility**.
- ***Mechanism of actions***; **Methylxanthines** have ***several*** **mechanisms**, the ***main*** **mechanisms** are;
  1) ***Inhibits*** **phosphodiesterase enzyme** → ***increase*** **cyclic adenosine monophosphate (cAMP)**;
     - *In* **smooth muscle** → ***relaxation*** **(bronchodilatation)**.
     - *In* **cardiac muscle** → ***contraction*** **(*increase* heart rate)**.
  2) ***Block*** **adenosine receptors**;
     - *In* **heart** → ***increase*** **heart rate**.
     - *In* **brain** → **Stimulant effect**.
- **Methylxanthines** have been used for **asthma** for ***more than*** **50 years**, but their use in ***recent years*** has ***declined markedly*** owing to the ***high risk*** of **severe life-threatening toxicity** and ***numerous*** **drug interactions**, as well as ***decreased*** **efficacy** ***compared with*** **ICSs** and **LABAs**.
- To ***reduce*** **toxicity** while ***maintaining*** **therapeutic efficacy**, ***selective*** **inhibitors** of *different isoforms* of **phosphodiesterase enzyme type-4 (PDE4)** were ***developed***; **Roflumilast** ***approved for*** **COPD**.

Theophylline (Quibron®)

- **Theophylline** [thee-OFF-i-lin] is a ***methylxanthine*** **bronchodilator agent**.
- **Theophylline** ***relieves*** **airflow obstruction** in **chronic asthma** and ***decreases*** its **symptoms**.
- **Theophylline** is available in ***short-*** and ***long-acting*** **formulations**.
- ***Dose***; ***Adjust according to concentration***.
  - **Adult**; 300–600 mg/day. - **Children**; Start at 10 mg/kg/day. - **Pediatric**; Start; 5 mg/kg/day.
- ***Side effects***; ***At therapeutic levels***; **Insomnia, GI upset** and **agitation**.
- ***Toxicity***; ***At high levels***: **Nausea, vomiting, CNS stimulation, headache, cardiac arrhythmias** and **seizures**.
- ***Drug interactions***; **Theophylline** is ***metabolized*** in the **liver** by **CYP1A2** and **CYP3A4**; It is subject to ***numerous*** **drug interactions**; ***such as*** **Ketoconazole**, **Cimetidine** and **Erythromycin** (***increase*** **Theophylline therapeutic effect**). **Phenytoin** and **Barbiturates** (***decrease*** **Theophylline therapeutic effect**).

Leukotriene Modifiers (LTMs)

- **Leukotrienes (LTs)** ***result from*** the *action of* **5-lipoxygenase enzyme** ***on*** **arachidonic acid**.
- **LTs** are ***synthesized by*** (*not stored*) a *variety of* **inflammatory cells** in the **airways**, *including* **eosinophils, mast cells, macrophages** and **basophils**.
  - **Leukotriene B$_4$ (LTB$_4$)**; is a ***potent*** **neutrophil chemoattractant**.
  - **Cysteinyl leukotrienes (LTC$_4$, LTD$_4$** and **LTE$_4$)**; are a ***potent*** **bronchoconstrictor** (1000 times more potent than histamine), ***increased*** **bronchial reactivity, mucosal edema,** and **mucus *hypersecretion***.
- **Bronchospasm** ***occur bout*** **10%** of **people taking NSAIDs**, ***because*** of a ***shift*** in **arachidonic acid** ***from*** **COX** ***to*** **5-LOX**.

Leukotriene Receptor Antagonists (LTRAs); Chronic Asthma

Zafirlukast (Accolate®)	**Montelukast** (Singulair®)	**Pranlukast** (Onon®)

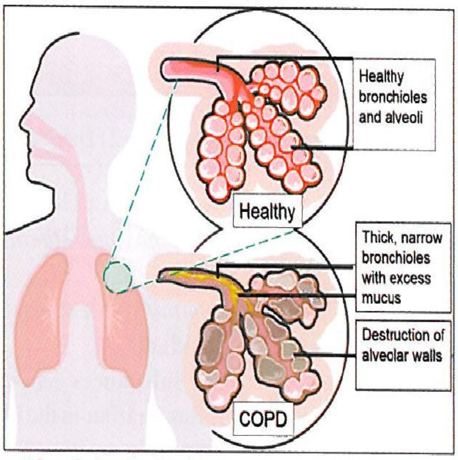
- **Zafirlukast** [ZA-fir-LOO-kast], **Montelukast** [MON-te-LOO-kast] and **Pranlukast** [PR-an-LOO-kast] are ***selective*** **antagonists** of the **cysteinyl leukotriene-1 receptor** (**CysLT$_1$ receptor** for **leukotrienes; LTC$_4$, LTD$_4$** and **LTE$_4$**).
- **Pranlukast** is ***widely used*** in **Japan** (*not available in United States and many other countries*).
- **Zafirlukast** and **Montelukast** ***used for*** the ***prophylaxis*** and **chronic** ***treatment*** of **asthma**.
- **Montelukast** ***used in*** **exercise-induced bronchospasm** and ***seasonal*** & ***perennial*** **allergic rhinitis**.

Intermittent asthma	Persistent asthma: 5–11 year olds				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred SABA *as needed*	*Preferred* *Low-dose* ICS *Alternative* LTRA OR Cromolyn OR Nedocromil OR Theophylline	*Preferred* *Medium-dose* ICS OR *Low-dose* ICS + LABA OR LTRA OR Theophylline	*Preferred* *Medium-dose* ICS + LABA *Alternative* *Medium-dose* ICS + LTRA OR Theophylline	*Preferred* *High-dose* ICS + LABA *Alternative* *High-dose* ICS + LTRA OR Theophylline	*Preferred* *High-dose* ICS + LABA + Oral corticosteroids *Alternative* *High-dose* ICS + LTRA OR Theophylline + Oral corticosteroids

Intermittent asthma	Persistent asthma: ≥12 year olds and adults				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred SABA *as needed*	*Preferred* *Low-dose* ICS *Alternative* LTRA OR Cromolyn OR Nedocromil OR Theophylline	*Preferred* *Medium-dose* ICS OR *Low-dose* ICS + LABA *Alternative* *Low-dose* ICS + LTRA OR Theophylline OR Zileuton	*Preferred* *Medium-dose* ICS + LABA *Alternative* *Medium-dose* ICS + LTRA OR Theophylline OR Zileuton	*Preferred* *High-dose* ICS + LABA AND Consider **Omalizumab** for patients who have *allergies*	*Preferred* *High-dose* ICS + LABA + Oral corticosteroids AND Consider **Omalizumab** for patients who have *allergies*

Chronic Obstructive Pulmonary Disease (COPD)

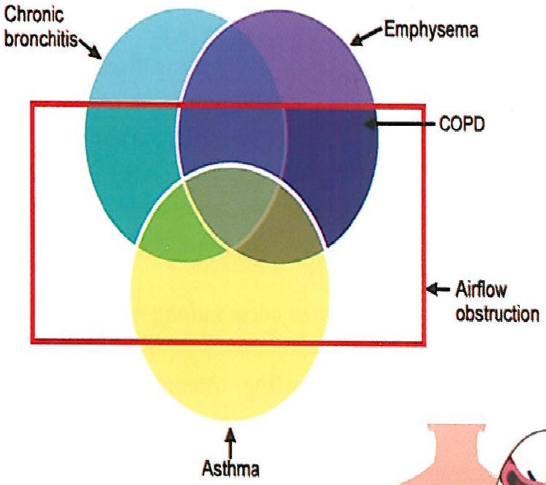
➢ Overview:-


Healthy bronchioles and alveoli
Healthy
Thick, narrow bronchioles with excess mucus
Destruction of alveolar walls
COPD

- **Chronic obstructive pulmonary disease** (**COPD**) is a *type* of **obstructive lung disease** *characterized by* ***long-term*** **poor airflow**.
- **COPD** ***typically*** **worsens** ***over time*** and **airflow obstruction** that is ***not fully*** **reversible**.
- **COPD** is *historically* ***described as***; **chronic bronchitis** or **emphysema**.
- The ***primary cause*** of **COPD** is **cigarette smoking**, ***implicated in*** **85%** of **diagnosed cases**.
- **COPD**, was the **third** ***leading*** **cause** *of* **death** in the **United States** in **2014**.

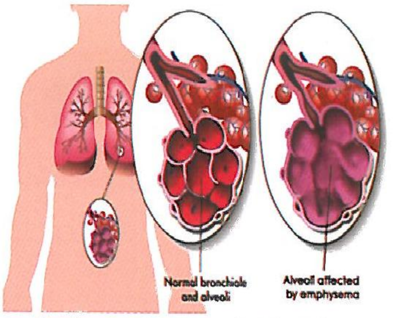
* * * * * **Emphysema**, **Chronic Bronchitis**, **Asthma** and **COPD** * * * * *

Emphysema	Chronic Bronchitis
Gradual damage of lung tissue (specifically thinning and destruction of the alveoli)	***long-lasting productive cough***
Asthma	**COPD**
Recurrent episodes of wheezing, breathlessness, cough and chest tightness	***Long-term poor airflow*** *with* **emphysema**, **chronic bronchitis** and in *some cases* **asthma**.


Chronic bronchitis
Emphysema
COPD
Airflow obstruction
Asthma

Venn diagram of COPD

➢ Definition:-


Normal bronchiole and alveoli
Alveoli affected by emphysema

- **COPD**; is a *syndrome* of ***chronic*** **limitation** ***in*** **expiratory airflow** *encompassing* **emphysema** and **chronic bronchitis**; **Airflow obstruction** *may be* ***accompanied by*** **airway hyperresponsiveness** and may be ***not be fully*** **reversible**.

  1) **Chronic bronchitis**; *consists of* ***persistent*** **cough** ***plus*** **sputum production** for ***most days*** of **3 months** in ***at least*** **2 consecutive years**.
  2) **Emphysema**; is ***abnormal permanent*** **enlargement** of the **airspaces distal** to the **terminal bronchioles**, *accompanied by* ***destruction of*** **their walls** and ***without*** **obvious fibrosis**.

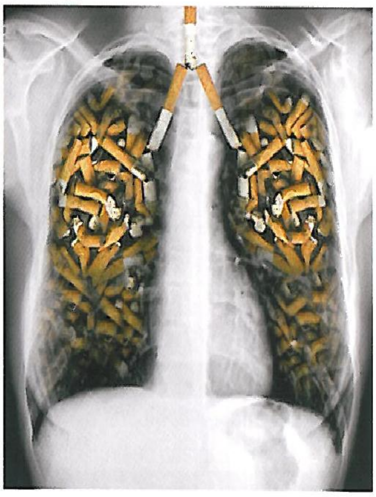
➢ Prevalence:-

- **COPD** ***affects*** **< 6%** of the **global population**.
- **COPD**, was the **third** ***leading cause of*** **death** in the **United States** in **2014**.
- In the **United States** *approximately* **15 million people,** have been ***diagnosed with*** **COPD**.
- It ***typically occurs in*** **people** ***over*** the age of **40**.

➢ Pathophysiology:-

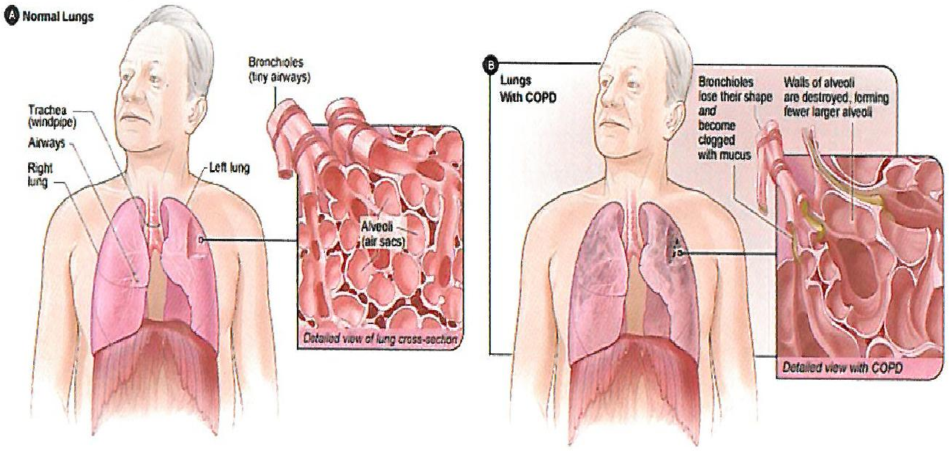
Cigarette smoking causes about 80%-90% of all COPD cases

1) Chronic inflammatory *changes* → 2) Destructive *changes* → 3) Chronic airflow *limitation*.



- **Oxidative stress**; ***most cases*** of **COPD** are the result of ***exposure*** to ***noxious stimuli***, most often **cigarette smoke**.
- **Cigarette smoke** ***contains*** an ***extremely*** **high concentration** of **oxidants**.
- The ***reactive*** **oxidant substances** *generated by* **smoking** ***induce*** **inflammation** in the **lung** and ***its*** **airway**.
- The **inflammatory cells** ***release*** a variety of **inflammatory mediators**, of which ***play*** **major roles** in the ***pathogenesis*** of **smoking-induced airflow limitation.**
- **Airflow limitation**; occurs *due to* **inflammation** and **scarring** ***within*** **them**.

- **Protease-antiprotease imbalance**; ***imbalance*** in the **lungs** of **COPD patients** *between* **proteases** that ***break down*** **connective tissue components** and ***antiproteases*** that **counterbalance** ***this*** **action**.
- **Mucus hypersecretion** is ***present*** **early** in the **disease** and is ***associated with*** an ***increased*** **number** and **size** of **mucus-producing cells**.
- **Gas exchange abnormalities**; may result in **hypoxemia** & **hypercapnia** in **COPD patients**.
- **Pulmonary hypertension** *may develop* ***late*** in the course of **COPD**.
- **Exacerbations**; **exacerbations** of ***respiratory symptoms triggered by*** **respiratory infections** (bacteria or viruses), **environmental pollutants**, or **unknown factors** often occur in ***patients with*** **COPD**.
- **Systemic features**; **COPD** often **occurs** ***along with*** a **number** of **other conditions**, due in part to ***shared risk factors***. These conditions include **ischemic heart disease**, **heart failure**, **diabetes mellitus**, **muscle wasting**, **osteoporosis**, **normocytic anemia**, and **metabolic syndrome**.


A Normal Lungs
Trachea (windpipe)
Airways
Right lung
Left lung
Bronchioles (tiny airways)
Alveoli (air sacs)
Detailed view of lung cross-section
B Lungs With COPD
Bronchioles lose their shape and become clogged with mucus
Walls of alveoli are destroyed, forming fewer larger alveoli
Detailed view with COPD

➢ Signs and symptoms:-

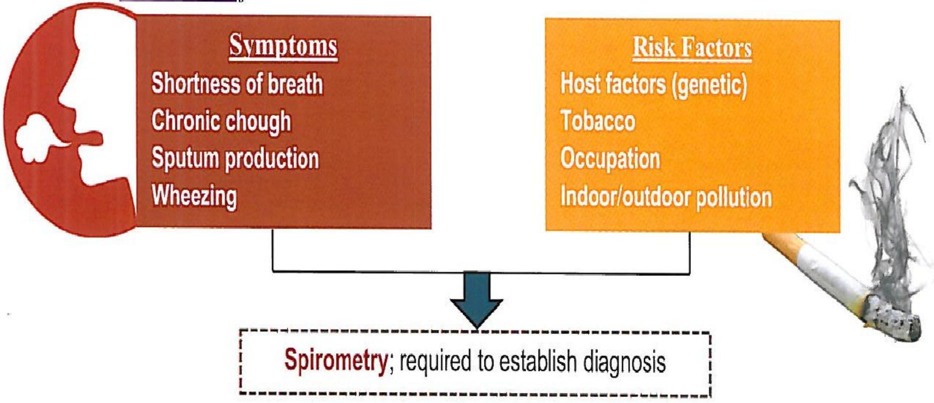
- **Cough**; usually *worse* in the *mornings* and *productive* of a small amount of colorless sputum.
- **Dyspnea** (shortness of breath); *worsens over time*, *persistent* (*present every day*), and *worse with* exercise.
- **Wheezing** and **chest tightness**.
- **Exacerbation**; acute exacerbation of COPD; *increased* shortness of breath, *increased* sputum production, a *change in the* color of the sputum *from* clear *to* green or yellow, or an *increase* in cough.

➢ Cause and Risk Factors:-

- **Cigarette Smoking**; tobacco smoking *accounts for* as *much as* 90% of COPD *risk*. Secondhand smoke, or environmental tobacco smoke; *increases* COPD *risk*.
- **Occupational exposures**; *Exposure to* organic and inorganic dusts, chemical agents and fumes are *risk factor* for COPD.
- **Environmental Factors**; *Long-term exposure* to traffic-related air pollution may be a factor in COPD in *patients with* diabetes and asthma.
- **Genetics**; *currently*, the *only* clearly inherited risk factor is alpha 1-antitrypsin deficiency (AAT).
- **Age** and **gender**; Age is often listed as a *risk factor* for COPD. Women are *more susceptible* to the effects of tobacco smoke *than* men.
- **Asthma**, **airway hyperreactivity** and **chronic bronchitis**; may be a *risk factor* for COPD.
- **Infections**; history of *severe* childhood respiratory infection and *susceptibility* to infections *plays* a role in COPD.

➢ Diagnosis:-

- **COPD** *should be* considered in *any* patient older than 40 years who has symptoms (dyspnea, chronic cough, sputum *production* or wheezing), and/or a *history of* exposure to risk factors *for the* disease.



- **Spirometry**; gold standard
  - FEV$_1$ *should be* measured *before* bronchodilator is *given*.
  - Bronchodilators are given (usual doses are 400 mcg of SABA, 160 mcg of short acting anticholinergic, or the two combined).
  - FEV$_1$ *should be* measured *again* 10-15 minutes after SABA or 30–45 minutes after short acting anticholinergic, or the two combined.
  - Results; FEV$_1$/FVC in *post-bronchodilator* < 70% *confirms* the presence of air flow limitation (COPD).
- **Classification of *severity of* airflow limitation**; Spirometric GOLD[a] Classification

Based on post-bronchodilator FEV$_1$ of predicted		
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50-79%
GOLD 3	Severe	30-49%
GOLD 4	Very severe	< 30%

[a] GOLD = Global Initiative for Chronic Obstructive Lung Disease

- **Assessment of symptoms**;

A) **Modified British Medical Research Council (mMRC) dyspnea scale**;

	ONE box only	
Grade 0	Dyspnea (shortness of breath) only with strenuous activity.	☐
Grade 1	Slight dyspnea with vigorous (hurrying) walking.	☐
Grade 2	Moderate dyspnea with normal walking.	☐
Grade 3	Severe dyspnea (stop berthing) after a few minutes of walking (*about* 100 meters).	☐
Grade 4	Very severe dyspnea with changing clothing.	☐

B) **COPD Assessment Test (CAT™)**;

Example: I am very happy ⓪ [✓ ①] ② ③ ④ ⑤ I am sad

			SCORE
I never cough	⓪ ① ② ③ ④ ⑤	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	⓪ ① ② ③ ④ ⑤	My chest is full of phlegm (mucus)	☐
My chest does not feel tight at all	⓪ ① ② ③ ④ ⑤	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	⓪ ① ② ③ ④ ⑤	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	⓪ ① ② ③ ④ ⑤	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	⓪ ① ② ③ ④ ⑤	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	⓪ ① ② ③ ④ ⑤	I don't sleep soundly because of my lung condition	☐
I have lots of energy	⓪ ① ② ③ ④ ⑤	I have no energy at all	☐
		YOUR TOTAL SCORE!	☐

Scores on CAT range from 0–40 with the higher the score, the more severe the disease
For online test (different languages), visit; www.catestonline.org

- **Frequency of exacerbations**; ***number*** **of acute exacerbations** ***per*** **year.**
- **Other tests**; **chest X-ray** and **CBC** (***higher*** **eosinophil counts** *may predict* **increased** exacerbation *rates*).
- **Differential diagnoses**; **COPD** may need to be ***differentiated from*** **other causes** of **shortness of breath** such as **congestive heart failure** (CHF), **pulmonary embolism**, **obliterative bronchiolitis** and **others**.

➢ Assessment of COPD Severity and Risk:- (GOLD Guidelines)

Patient Group	Characteristic	Spirometric GOLD Classification	Exacerbations per Year	Symptom Score
A	Low risk Fewer symptoms	GOLD 1: Mild (≥80%) GOLD 2: Moderate (50-79%)	Number; ≤1 No hospitalization	mMRC; 0–1 CAT; <10
B	Low risk More symptoms	GOLD 1: Mild (≥80%) GOLD 2: Moderate (50-79%)	Number; ≤1 No hospitalization	mMRC; ≥2 CAT; ≥10
C	High risk Fewer symptoms	GOLD 3: Severe (30-49%) GOLD 4: Very severe (< 30%)	Number; ≥2 or ≥1 With hospitalization	mMRC; 0–1 CAT; <10
D	High risk More symptoms	GOLD 3: Severe (30-49%) GOLD 4: Very severe (< 30%)	Number; ≥2 or ≥1 With hospitalization	mMRC; ≥2 CAT; ≥10

➢ Managements:-

- *Treatment Goals*;
  1) ***Relieve*** **symptoms.**
  2) ***Reduce*** the **frequency** and **severity** of **exacerbations.**
  3) ***Improve*** **exercise tolerance.**
  4) ***Improve*** **health status.**
  5) ***Minimize*** **adverse effects** ***from*** **treatment.**

You can do it.

Smoking Cessation Therapies

- **Smoking cessation** is the ***most important*** **therapeutic intervention** for **COPD**.
- **Smoking cessation** has the ***greatest capacity*** to **influence** the **natural history** of **COPD**.
- ***Long-term*** **quit smoking** ***success rates*** of ***up to*** **25%** can be ***achieved***.

Nicotine Replacement Therapies

Nicotine (Nicorette®)

Agent	Usual Dose	Duration	Common Side Effects
Nicotine gum	2–4 mg gum prn, up to 24 pieces daily	12 weeks	Sore mouth, dyspepsia
Nicotine inhaler	6–16 cartridges daily	Up to 6 months	Sore mouth and throat
Nicotine nasal spray	8–40 doses daily	3–6 months	Nasal irritation
Nicotine patches	7–21 mg every 24 hours	Up to 8 weeks	Skin reaction, insomnia

- Nicorette® products (chewing gum, lozenges, patches, oral spray inhalator, sublingual tablets and nasal spray) ***aid in smoking cessation***.
- **Nicotine replacement therapy** ***should be*** **started > 2 weeks** ***after*** a **cardiovascular events** (such as acute coronary syndrome).
- The ***effectiveness*** and ***safety*** of **e-cigarettes** as a **smoking cessation** ***aid*** is ***uncertain at*** present.

Varenicline

Varenicline (Chantix®) (Champix®)

- Chantix® in the USA and Champix® in Canada Europe and other countries.
- **Varenicline** [var-EN-ih-kleen] is an **oral drug** ***used to*** **quit smoking** ***(treat nicotine addiction)***. ***Act as*** a **partial agonist** in the **nicotinic receptors** (*especially CNS*).
- ***Dose***;
  - **Days 1 to 3** ⇨ 0.5 mg orally once a day.
  - **Days 4 to 7** ⇨ 0.5 mg orally twice a day.
  - **Days 8 to end of treatment** ⇨ 1 mg orally twice a day.
    - ☞ Patients ***should be*** treated with **Varenicline** for **12 weeks**.
- ***Most common adverse effects*** ☞ **Nausea, vomiting, headache, constipation, sleep disturbance** and **unusual dreams**. **Varenicline** are **category C** ***in pregnancy***.

Bupropion

Bupropion (Wellbutrin®)

- **Bupropion** [byoo-PROE-pee-on] is a ***weak*** **norepinephrine-dopamine *reuptake* inhibitor** (**NDRI**), the ***exact* mechanism** of action remains **unknown**.
- ***Dose***;
  - ***Initial dose***; 150 mg orally once daily for 3 days.
  - ***Maintenance dose***; 150 mg orally twice a day.
  - ***Duration of therapy***; **12 weeks**, up to 6 months.
- ***Most common* side effects**; ***increased* risk of seizures, insomnia, anxiety, irritability, headache**, and ***decreased* appetite**.
- ***Warning***; **Bupropion *should not be* prescribed** to individuals with **epilepsy** or other conditions that ***lower*** the **seizure threshold**.

Vaccinations

All patients with* COPD *should receive the **influenza vaccine** ***yearly*** and the ***polysaccharide*** **pneumococcal vaccine** ***once before*** **age 65**; then a **one-time *revaccination*** **5** years or ***more after*** the ***first*** **vaccination**.

Pharmacologic Therapy for Stable COPD

See previous topic (Asthma) for more drug details

Bronchodilator Medications

- ***Bronchodilator Medications*** in **COPD**;
  1) **β_2-agonists**
  2) **Anticholinergics**
  3) **Methylxanthines**
  4) ***Combination bronchodilator therapy***; **β_2-agonists** + **Anticholinergics**
- ***Recommendations***;
  - * ***All* bronchodilators *improve*** **symptoms** and **exercise *capacity***.
  - * The ***choice between*** a **LABA**, **Anticholinergic**, **Theophylline**, and ***combination therapy depends on***; **1)** **Availability**. **2)** **Individual response in symptom *relief***. **3)** **Adverse effects**.
  - * ***Combining* bronchodilators** from ***different*** **pharmacologic classes** may ***improve* efficacy** with the **same** or ***fewer*** **adverse effects *compared with*** **increasing** the **dose** of a ***single*** **bronchodilator**.
  - * **Inhaled therapy** is ***preferred***.

β_2-agonists

Short-acting β_2-adrenoceptor Agonists (SABA); 4-6 hours

Salbutamol or Albuterol (Ventolin®)	**Levosalbutamol or Levalbuterol** (Xopenex®)
Terbutaline (Bricanyl®)	**Pirbuterol** (Maxair ®)

Long-acting β_2-adrenoceptor Agonists (LABA); 12 hours

Formoterol (Foradil®)	**Salmeterol** (Serevent®)	**Arformoterol** (Brovana®)

Ultra-Long-acting β_2-adrenoceptor Agonists (Ultra-LABA); 24 hours

Indacaterol (Onbrez® Breezhaler®)	
Olodaterol (Striverdi® Respimat®)	**Vilanterol** (Breo® Ellipta®) (Anoro® Ellipta®)

- **Vilanterol** [vye-LAN-ter-ol] is the ***only*** **ultra-LABA** ***not available*** by **itself** but as a ***component*** of **combination drugs**;
    1) **Breo® Ellipta®**; with **Fluticasone furoate** (**inhaled corticosteroid**); *approved for* **COPD** and **chronic asthma**.
    2) **Anoro® Ellipta®**; with **Umeclidinium bromide** (**long-acting anticholinergics**); *approved for* **COPD**.
- ***Recommendations***;
    - * ***Regular treatment*** with a **LABAs** (*include* ultra-LABA) is ***more effective*** and ***convenient than*** **regular treatment** with **SABAs**.
    - * **LABAs** ***improve*** **health status, quality of life,** and FEV_1 and ***decrease*** **COPD exacerbation rate**.
    - * **LABAs** have ***no effect*** on **mortality** and **rate of decline** of **lung function**.
    - * **Salmeterol** ***reduces*** **hospitalization rate**.
    - * **Indacaterol** ***significantly improves*** **breathlessness, health status** and **exacerbation** ***rate***.
    - * **Indacaterol** has a ***significantly*** **greater bronchodilator effect** ***than*** **Formoterol** and **Salmeterol** and a **bronchodilator effect** ***similar to*** that of **Tiotropium**.
    - * **LABAs** ***do not have*** the **same potential safety** ***concerns as with use in*** **asthma**.

Anticholinergics

Short-acting Muscarinic Antagonist (SAMA); <12 hours

Ipratropium (Atrovent®)	**Oxitropium** (Oxiven®)

Long-acting Muscarinic Antagonist (LAMA); 12-24 hours

Tiotropium (Spiriva®)	**Umeclidinium** (Incruse® Ellipta®)
Aclidinium (Tudorza®)	**Glycopyrronium** (Seebri® Breezhaler®)

- ***Recommendations***;
    - * **Ipratropium** (**SAMA**) ***provided*** **small benefits** ***over*** **SABA** in **terms** ***of*** **lung function, health status** and ***requirement for*** **oral steroids**.
    - * **LAMAs administration**;
        - **Once a day**; **Tiotropium** and **Umeclidinium**. - **Twice a day**; **Aclidinium**.
        - **Once daily** dosing *in some countries* and **twice daily** dosing *in others*; **Glycopyrronium**.
    - * **LAMAs VS LABAs**;
        - **Tiotropium** is ***more effective*** *than* **Salmeterol** as ***initial*** **long-acting bronchodilator therapy** in ***moderate*** to ***very severe*** **COPD** ***regarding time*** to **first exacerbation** and ***annual number*** of **exacerbations**.
        - **Tiotropium** is ***more effective*** *than* **LABAs** in ***preventing*** **COPD** ***exacerbations*** and **COPD-*related hospitalization*** (but not in overall hospitalization or mortality).

Methylxanthines

Theophylline (Quibron®)

- ***Recommendations***;
    - * ***Efficacy*** of **Theophylline** in **COPD** were ***performed with*** **sustained-release** ***preparations***.
    - * **Theophylline** has ***modest*** **bronchodilator** ***effect*** *compared with* **placebo** in **stable COPD**.
    - * ***Addition*** of **Theophylline** to **Salmeterol** ***produces*** a ***greater*** **improvement** in FEV_1 and **breathlessness** *than* **Salmeterol** ***alone***.

Combining Bronchodilators

Product	β2-agonist	Anticholinergic
Combivent®	**Salbutamol** (SABA)	**Ipratropium** (SAMA)
Atrovent® Comp	**Fenoterol** (SABA)	**Ipratropium** (SAMA)
Duaklir® - Brimica®	**Formoterol** (LABA)	**Aclidinium** (LAMA)
Bevespi Aerosphere®	**Formoterol** (LABA)	**Glycopyrronium** (LAMA)
Utibron® Neohaler®	**Indacaterol** (LABA)	**Glycopyrronium** (LAMA)
Anoro® Ellipta®	**Vilanterol** (LABA)	**Umeclidinium** (LAMA)
Stiolto® Respimat®	**Olodaterol** (LABA)	**Tiotropium** (LAMA)

- ***Recommendations***;
  - * ***Combinations*** of **SABAs** and **SAMAs** are **superior** ***compared*** to ***either*** **medication** ***alone*** in ***improving*** FEV$_1$ and **symptoms.**
  - * ***Combinations*** of **Formoterol** and **Tiotropium** in has a ***bigger impact*** on **FEV$_1$** *than* ***either*** **component** ***alone***.
  - * ***Combinations*** of a **LABAs** and **LAMAs** ***improve*** **lung function** ***compared to*** **monotherapy** *alone*.
  - * ***Combinations*** of a **LABAs** and **LAMAs** ***decreased*** **exacerbations** to a **greater extent** ***than*** **LABAs** and **ICS** **combination.**

Anti-inflammatory Agents

Inhaled Corticosteroids (ICSs)

Beclomethasone (QVAR®)	**Fluticasone** (Flovent®) (Flixotide®)
Mometasone (Asmanex®)	**Budesonide** (Pulmicort® Flexhaler) (Miflonide®)
Triamcinolone (Azmacort®)	**Flunisolide** (Aerospan®)
Ciclesonide (Alvesco®)	

- ***Recommendations***;
  - * **ICSs** ***improve*** **symptoms, lung function**, and **quality of life** and ***decrease*** the **frequency** of **exacerbations in patients** ***with*** **FEV$_1$** ***less than*** **60%** of predicted.
  - * The ***dose response*** with **ICS** in **COPD** is ***unknown*** (*in contrast to* **asthma** ***treatment***).
  - * ***Combinations*** of **ICS** and **LABA** is ***more effective*** *than* the **individual components.**
  - * ***Combinations*** of **ICS** and **LABA** ***reduces*** the **rate** of ***decline*** of **FEV$_1$** and ***reduces*** the **exacerbation rate.**
  - * ***Long-term*** **monotherapy** with **ICSs** is ***not recommended***; they are ***less effective*** than **ICS/LABA** ***combination***.
  - * ***Regular*** *treatment with* **ICS** ***increase*** the **risk of pneumonia** *especially* in those with ***severe*** **COPD.**
- **β_2-Agonist/Inhaled Corticosteroid Combinations**;

Product	Corticosteroid	β_2-Agonist
Symbicort®	**Budesonide**	**Formoterol**
Dulera®	**Mometasone**	**Formoterol**
Fostair®	**Beclomethasone**	**Formoterol**
Advair® - Seretide®	**Fluticasone**	**Salmeterol**
Breo® Ellipta®	**Fluticasone**	**Vilanterol**

Triple Inhaled Therapy (ICS/LABA/LAMA)

- ***Recommendations***;
  - * ***Triple therapy*** **ICS/LABA/LAMA** ***improve*** **lung function**, **symptoms** and **health status** and ***reduce*** **exacerbations** ***compared to*** **ICS/LABA** or **LAMA** ***monotherapy***.
- ***Products***;
  - Triohale® pressurized Metered-Dose Inhaler (pMDI); **Ciclesonide/Formoterol/Tiotropium** has been marketed as the ***world's first*** **triple-combination inhaler** to be taken only **once** a **day** and is already available in **India.**
  - ....®; **Fluticasone Furoate/Umeclidinium/Vilanterol**; ***Preregistration*** by **GSK.**
  - ....®; **Mometasone/Indacaterol/Glycopyrronium**; ***Preregistration*** by **Novartis.**
  - ....®; **Budesonide/Formoterol/Glycopyrronium**; ***Preregistration.***
  - ....®; **Beclomethasone/Formoterol/Glycopyrronium**; ***Preregistration.***

Oral Glucocorticoids (OCSs)

- ***Recommendations***;
  - * ***Chronic treatment*** with **OCSs** ***should be*** **avoided** because of an ***unfavorable*** **benefit-risk ratio.**
  - * **OCSs** used treating ***acute exacerbations*** in **hospitalized patients**, or ***during*** **emergency.**

Phosphodiesterase-4 (PDE4) inhibitors

Roflumilast (Daxas®) (Daliresp®)

- **Roflumilast** [roe-FLUE-mi-last] is a ***phosphodiesterase-4 inhibitor***, is an ***anti-inflammatory***, ***not*** **bronchodilator**.
- *Mechanism*; ***Reduces*** **inflammation** through ***inhibition*** of the **breakdown** of **intracellular cyclic adenosine monophosphate (cAMP)**, ***no*** **direct bronchodilator activity**.
- *Indication*: ***reduce*** the ***risk*** of **COPD exacerbations** in ***patients with*** **severe COPD** ***associated with*** **chronic bronchitis** and a **history of exacerbations**.
- *Dose*; **500 mcg orally** ***once daily***.
- *Side effects*; **Diarrhea, weight loss** (*monitoring body weight*) or ***decreased*** **appetite, nausea, headache, back pain, influenza, insomnia** and **dizziness**.
- *Contraindications*: ***Moderate*** to ***severe*** **liver impairment**.
- *Drug interactions*: With ***strong*** **CYP450 enzyme** ***inducers*** or ***inhibitors***.
- *Recommendations*;
  - * A **PDE4 inhibitor** ***improves*** **lung function** and ***reduces*** **moderate to severe exacerbations**.
  - * A **PDE4 inhibitor** ***improves*** **lung function** and ***decreases*** **exacerbations** in **patients** who are on ***fixed-dose*** **LABA/ICS combinations**.

Other Pharmacological Treatments

Antibiotics

Azithromycin

Erythromycin

- *Recommendations*;
  - * **Azithromycin** (250 or 500 mg/day three times per week) or **Erythromycin** (500 mg two times per day) for ***one year*** in **patients** ***prone to*** **exacerbations** ***reduced*** the ***risk of*** **exacerbations** *compared to* **usual care**.
  - * **Azithromycin** use was ***associated with*** an ***increased*** *incidence of* **bacterial resistance** and ***impaired*** **hearing tests**.

Mucolytic and Antioxidant Agents

- In **COPD patients** ***not receiving*** **inhaled corticosteroids**, ***regular treatment*** with **Mucolytics** such as **Carbocysteine** and **N-acetylcysteine (NAC)** may ***reduce*** **exacerbations** and ***improve*** **health status**.
- *Recommendations*;
  - * ***Regular*** use of **NAC** and **Carbocysteine** ***reduce*** the ***risk of*** **exacerbations** in **selected patients**.

Alpha-1 Antitrypsin Augmentation Therapy

Alpha-1 Proteinase Inhibitor (Zemaira®)

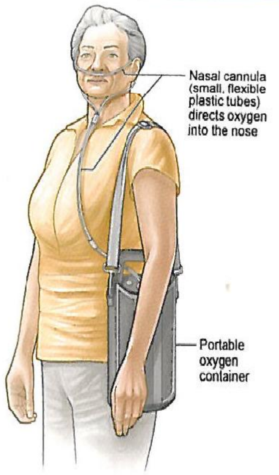
- **Patients** ***with*** **α_1-antitrypsin deficiency (AATD)** ***usually*** **are white**, usually ***develop*** **COPD** at a **young age (younger than 45 years)**, and have a ***strong*** **family history**.
- **IV** ***augmentation therapy*** has been ***recommended for*** *individuals with* **AATD**.
- *Recommendations*;
  - * **IV** ***augmentation therapy*** may ***slow down*** the ***progression of*** **emphysema**.

Long-term treatment with β-blockers reduces risk of exacerbations and improves survival, even in patients without overt cardiovascular disease. Mechanism for benefit in COPD is unknown, but β-blockers can upregulate β2-receptors in the lungs, which may improve the effectiveness of inhaled β-agonists. It is too early to recommend β-blockers for the treatment of COPD, but β-blockers should not be withheld in patients with COPD who also have heart disease, chronic heart failure, or other cardiovascular conditions in which β-blockers are beneficial.

Non-pharmacologic Therapy

Home Oxygen Therapy & Home Oxygen Concentrators

- **Oxygen therapy** *should be* ***considered for*** *any* **patient** with **hypoxemia** ***during*** an **exacerbation**.
- **Oxygen therapy** *should be* used to ***achieve*** a **Pa_{O_2}** of ***greater than*** **60 mm Hg** or **oxygen saturation** (Sa_{O_2}) of ***greater than*** **90%**.
- ***Recommendations***;
  - * ***Recommended*** in **patients** who have a **Pa_{O_2}** of **55 mm Hg** or ***less*** or **Sa_{O_2}** of **88%** or ***less***.


Nasal cannula (small, flexible plastic tubes) directs oxygen into the nose
Portable oxygen container

Pulmonary Rehabilitation

- *Includes* **exercise training**, **nutrition counseling**, and **education**.
- *Improves* many **outcomes** in **COPD**, *including* **quality of life** and **survival**.

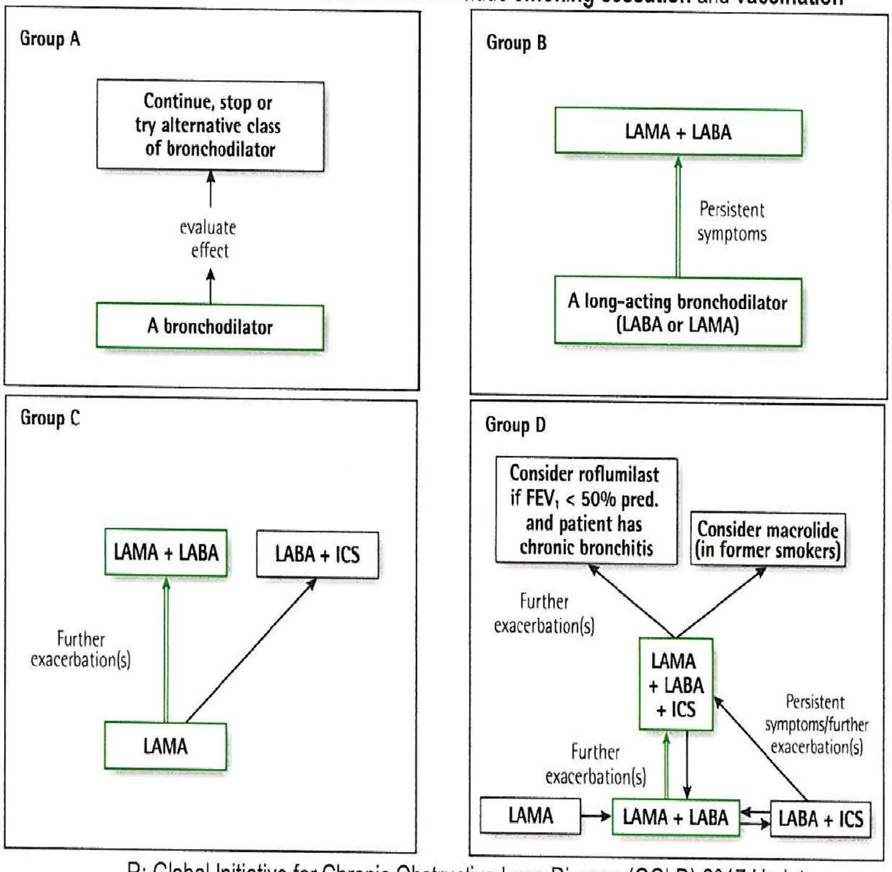
Surgery

- **Lung volume reduction surgery**; *removing* the **parts** of the **lung** ***most damaged by*** **emphysema** *allowing* the **remaining, relatively good lung** to **expand** and *work* **better**.
- **Lung transplantation**; *performed* for ***very severe*** **COPD**, particularly in **younger individuals**.

Guidelines

- **Stable Chronic COPD:-** ⟹ = Preferred agents

Prevention and risk *reduction* efforts include **smoking cessation** and **vaccination**


Group A
Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)
Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA
Group D
Consider roflumilast if FEV₁ < 50% pred. and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS

R; Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 Update

➢ Acute Exacerbations of Chronic COPD Management:-

Mild

Inhaled short acting bronchodilators
SABA with or without SAMA

Moderate

***Add* antibiotics and/or oral corticosteroids**

Severe

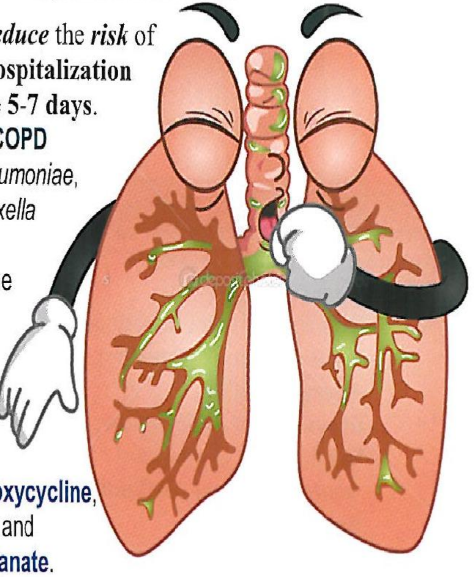
Patient requires hospitalization or visits the emergency room

- *Recommendations*;

  * **Inhaled Bronchodilators** (*inhaled* **SABAs** *with* or *without* **SAMA**) are the **preferred** treatment of **COPD exacerbations**;
    - **MDI inhaler one *puff*** *every* **one hour** for **two** or **three *doses*** and then ***every* 2-4 hours** based on the **patient's response**.
    - ***Short-acting anticholinergics*** (**Ipratropium**) are ***generally*** added for **acute exacerbation**.

  * **Systemic Corticosteroids** are *effective*, and they ***shorten*** **recovery time**, ***improve*** **FEV$_1$**, and ***improve*** **oxygenation**; ***duration of therapy should not*** be ***more than*** **5-7 days**.
    - **OCS**; 40 mg **Prednisone** per day for **5 days** is ***recommended***.

  * **Antibiotic** can ***shorten*** **recovery time**, ***reduce*** the ***risk*** of **early relapse, treatment failure,** and **hospitalization** *duration*; ***duration of therapy should*** be **5-7 days**.
    - The ***most common*** **pathogens** in **COPD exacerbations**: *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*.
    - ***Recommended*** if **two** or **more** of the *following* are ***present***:
      1) ***Increased*** **dyspnea**.
      2) ***Increased*** **sputum *production***.
      3) ***Increased*** **sputum *purulence***.
    - *If* **uncomplicated COPD**; use **Azithromycin, Clarithromycin, Doxycycline, Trimethoprim/Sulfamethoxazole**, and **Amoxicillin**, *with* or *without* **Clavulanate**.
    - *If* ***complicated*** **COPD** with ***risk factors***: use **Amoxicillin/Clavulanate** or **Levofloxacin**, **Moxifloxacin**.
    - If **exacerbation *does not*** **respond** to **initial antibiotic**, **sputum culture** and ***sensitivity*** should be ***performed***.



  * **Methylxanthines** are ***not recommended***.

  * **Controlled Oxygen Therapy**; ***Titrate*** **oxygen** to *desired* **oxygen saturation** (>90%).

  * **Non-invasive Ventilation** (**NIV**); ***administration*** of **ventilatory support *without*** using an **invasive artificial airway**;
    - ***Consider*** *for patients with* **acute respiratory failure**.

Cough

➢ Overview:-

- **Cough**; is a ***defense mechanism*** that ***clear*** the **respiratory tract** *from* **mucus** and **irritants** such as **dust** or **smoke.**
- **Coughing** is either ***voluntary*** or ***involuntary***.
- **Cough reflex** is ***stimulated from*** **afferent cough receptors** *located in* the **upper** and **lower respiratory tract**, **pericardium**, **esophagus**, **diaphragm** and **stomach.**
- **Acute cough** (***less than*** **3 weeks**) is typically caused by **upper respiratory tract infection (URTI)**, or **common cold**, and is ***benign*** and ***self-limiting***.
- **Chronic cough** (***longer than*** **8 weeks**) has **multiple** potential ***underlying*** causes.
- **Pertussis** (**whooping cough** or **100-day cough**); is a *highly* ***contagious*** **bacterial disease** (*Bordetella pertussis*) and can ***lead to*** **life-threatening complications**. **Pertussis** is the ***only*** **vaccine-preventable** ***illness***.
- **BEFORE treating cough**; ***identification*** of its **cause** is **important** to ***ensure*** that **antitussive treatment** is ***appropriate***. The ***priority*** should always be to **treat** the ***underlying cause*** of **cough** *when* **possible.**

➢ Classification:-

- ***According to*** **durations**;
  - **Acute** (***sudden onset***); if it is present ***less than*** **3 weeks.**
  - **Subacute**; if it is present ***between*** **3** and **8 weeks.**
  - **Chronic**; when **lasting** ***longer than*** **8 weeks.**

Acute 3 weeks| **Subacute** 8 weeks| **Chronic**

- ***According to*** **character**;
  - **Dry**; ***non-productive*** (***no*** **phlegm** or **mucus** or **sputum** is **produced**).
  - **Productive** or **wet**; **coughs** that ***produce*** **phlegm** or **mucus** or **sputum.**

Acute Cough

- ***Duration***; ***less than*** **3 weeks.**
- ***Most common causes***;
  - **Respiratory tract infections (RTIs)**; *such as* **viral infections** (**common cold** and **influenza**), **sinus infections (sinusitis)**, **acute bronchitis**, **pneumonia** or **whooping cough.**
  - **Allergic rhinitis.**
  - **Laryngitis** or **pharyngitis.**
  - **Inhaled dust** or **smoke.**
  - ***Acute attacks of***; **asthma**, **chronic obstructive pulmonary disease (COPD)** or **chronic bronchitis.**
- **N.B.**; The ***majority of cases*** of **acute coughs** are *due to* the **common cold.**

Chronic Cough

- ***Duration***; ***longer than*** **8 weeks.**
- ***Most common causes***;
  - **Respiratory tract infections**, such as **bacterial infection** (**chronic bronchitis**, **chronic sinusitis**, **pneumonia** or **tuberculosis**).
  - ***Postinfectious*** **cough** *after* an **acute viral infection.**
  - **Asthma** and **COPD.**
  - **Allergies.**
  - **Medications; Angiotensin Converting Enzyme (ACE) Inhibitors.**
  - **Gastro Esophageal Reflux Disease (GERD).**
  - **Cystic fibrosis**, **emphysema**, **heart failure** and **lung cancer.**

Dry Cough

- *Most common causes*;
  - **Viral infections.**
  - **Environmental irritation, cigarette smoke** or **allergies.**
  - **Asthma.**
  - **Gastro Esophageal Reflux Disease (GERD).**
  - *Medications*; **Angiotensin Converting Enzyme (ACE) Inhibitors.**
- *Treatments*; **Antitussive.**

Productive (wet) Cough

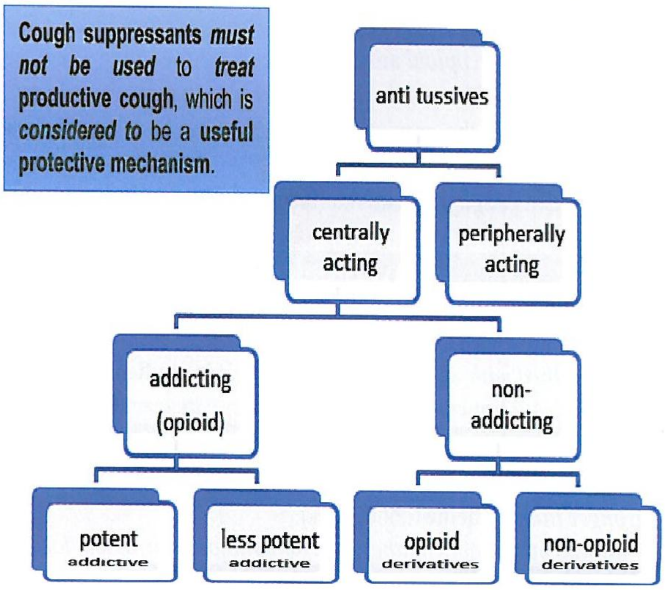
- *Most common causes*;
  - **Viral** or **bacterial infections.**
  - **COPD.**
  - **Chronic bronchitis.**
- *Treatments*; **Expectorants** and **Mucolytics.**

➢ Managements:-

- *Recommendations*;
  - ***No evidence*** **supporting** the ***effectiveness*** of a *most of* the ***common*** **OTC** and **prescription drugs** used to treat **acute cough.**
  - The **cough** ***associated with*** **upper respiratory tract infection** (**URTI**) ***typically resolves*** or is ***improving*** *within* **14 days**, although it can *last for* ***up to*** **3** or **4 weeks.**
  - The **FDA** ***does not*** **recommend OTC cough** and **cold drugs** (containing nasal decongestants, antihistamines, cough suppressants and expectorants) for use in **children** ***younger than*** **6** years for ***treatment of*** **URTI symptoms.**
  - *Acute* **bacterial infection** such as **pneumonia** *may require* **antibiotics.**
  - *Avoid prescribing* **antibiotics** for ***uncomplicated*** **acute cough.**
  - **Opioid cough drugs** have long been ***touted as*** the **gold standard** *of* **cough therapy.**
  - **Bronchodilators; β2 agonists** ***not recommended*** for the **treatment** of **acute cough** in the **non-asthmatic patient**, while **Ipratropium** ***improves*** **acute** and **chronic cough.**
  - *First generation* **antihistamines** are ***now can be used as*** **antitussives.**
  - **Cough** *caused by* **allergies** can be *treated by* ***avoiding*** **triggers** and taking **antihistamines.**
  - **Chronic cough** *due to* **GERD** can be *treated by* **Proton Pump Inhibitors (PPIs).**
  - ***For children***, the ***only*** **products** that can be **beneficial** are **Honey** (older than 1 year) and **VaporRub®** (older than 2 year).
- *Medications*;

Antitussives or Cough Suppressants

Cough suppressants ***must not be used*** to ***treat*** **productive cough**, which is *considered to* be a useful protective mechanism.



Central Antitussives

- *Mechanism of action*;

1) *Depression* of **medullary cough center**. 2) *Increased* **threshold** of **cough center**.

Opioid/Narcotic/Addicting Antitussives

Potent Addictive Opioids

Morphine

- **Morphine** [MOR-feen] is a ***natural*** **opioid alkaloid** has had a long ***history*** of use as an **antitussive**.
- **Morphine** is a ***strong opioid agonist***.
- **Morphine** ***should be*** **used for** ***severe*** **cough** ***not*** **suppressed** by **Codeine** or ***others***; *due to serious* **side effects,** *particularly* **respiratory depression, constipation** and **dependence.**
- *Dose*; **5-10 mg orally** ***every*** **4 hours** (or 2.5 - 5 mg SC/IV every 4 hours); **Cough suppression** occur with ***low doses*** of **opioids** than those ***needed for*** **analgesia**. - *Pregnancy category*; **C**.

Ethylmorphine

- **Ethylmorphine** [eth-yl-MOR-feen] is a ***narcotic analgesic*** and **antitussive**, also *known as* **Codethyline** and **Dionine**.
- **Ethylmorphine** is ***metabolized by*** the **liver** into **Morphine** by **ethylmorphine-N-demethylase** and ***used as*** an **indicator** of **liver function**.
- **Ethylmorphine** is ***used as*** an **antitussive** in ***some countries*** which is available in **cough syrup preparations** in ***combination with*** **Guaifenesin** or **Ephedrine** or with **Codeine**.
- *Dose*; **10-30 mg orally** ***every*** **4 hours** - *Pregnancy category*; **C**.

Hydromorphone

- **Hydromorphone** [HYE-droe-MOR-fone] is a ***semi-synthetic*** **Morphine** ***derivative***, is ***hydrophilic like, more*** **water soluble** ***than*** **Morphine**.
- **Hydromorphone** is a ***strong opioid agonist***.
- **Hydromorphone** and **Guaifenesin** ***combination*** is known under brand name Dilaudid® cough syrup.
- *Dose*; **1-2 mg orally** ***every*** **4 hours.** - *Pregnancy category*; **C**.

Less Addictive Opioids

Codeine

- **Codeine** [KOE-deen] (**3-Methyl-Morphine**) is a ***natural*** **opioid** with ***weak opioid agonist.***
- **Codeine** is *converted to* **Morphine** by the **CYP2D6 enzyme** in the liver.
- It is ***more selective*** *for* **cough center** (**Codeine** is the **gold-standard** ***antitussive***).
- ***Suppresses*** **cough** *for* ***about*** **6 hours**.
- ***Less*** **side effects** *than* **Morphine**.
- *Dose*; **10-20 mg** ***every*** **4-6 hours** (sub-analgesic dose) - *Pregnancy category*; **C**.

Pholcodine

- **Pholcodine** [FAHL-koh-deen] is an ***opioid*** **antitussive**, with ***mild*** **sedative effect**, but has ***little*** or ***no*** **analgesic effects**, also *known as* **Morpholinylethylmorphine** and **Homocodeine**.
- **Pholcodine** ***now*** **largely replaces** the ***previously more common*** **Codeine**, as it has a ***much lower*** *potential for* **dependence**.
- **Pholcodine** is found in certain ***cough medications*** (**lozenges** and **syrup**).
- *Dose*; **5-15 mg orally 3-4 times daily.** - *Pregnancy category*; **A**.

Dihydrocodeine

- **Dihydrocodeine** [dye-HYE-droe-koh-deen] is an ***opioid*** **antitussive**, it was *developed for* ***more effective*** **antitussive**, and it is ***twice*** as ***strong as*** **Codeine**.
- **Dihydrocodeine** are ***combined with*** **one** or **more** *other* **active ingredients**.
- *Dose*; **5-15 mg orally** ***every*** **4-6 hours.** - *Pregnancy category*; **C**.

Hydrocodone

- **Hydrocodone** [HYE-droe-KOE-done] is a ***semi-synthetic*** **Codeine** ***derivative.***
- **Hydrocodone** is ***stronger than*** **Codeine** (about 50%).
- **Hydrocodone** and **Homatropine** (*anticholinergic*) ***combination*** is *available for* **cough**.
- *Dose*; **1-2 mg orally** ***every*** **4-6 hours.** - *Pregnancy category*; **C**.

Non-Addictive Opioids

Dextromethorphan

- **Dextromethorphan** [deks-troe-meth-OR-fan] is *free* of **addictive properties** and produces *less* **constipation** than **Codeine**.
- It is *one* of the **active ingredients** in *many* **OTC cough medications**.
- The *primary use* of **Dextromethorphan** is as a **cough suppressant** (*antitussive*).
- **Dextromethorphan** is the *most commonly* **used** *agent* as **antitussive**.
- *Dose*; **15-30 mg orally** *every* **6-8 hours.** - *Pregnancy category*; **C**.
- At *high* **doses Dextromethorphan** acts as an **NMDA receptor** *antagonist* (**Hallucinations**).
- **Dextromethorphan** and **Codeine** are *available alone* or in *combination with* **Guaifenesin**.

Noscapine

- **Noscapine** [nos-ka-peen] is a *non-narcotic* **alkaloid** *derived from* **opioids**, with *mild* **analgesic, antitussive**, and *potential* **antineoplastic** *activities*.
- **Noscapine**, and its *synthetic derivatives* called **Noscapinoids** (**new class** of **anticancer drugs**) are known to *interact with* **microtubules** and *inhibit* **cancer cell** *proliferation*.
- *Dose*; **15-30 mg orally 3-4 times daily.** - *Pregnancy category*; **X**.

Levopropoxyphene (Novrad®)

- **Levopropoxyphene** [lee-voe-proe-POX-ih-feen] is an **antitussive**.
- It is the *levo isomer* of **Propoxyphene** (Darvon®); **opiate analgesic**.
  - **Dextropropoxyphene** has an *analgesic effect*.
  - **Levopropoxyphene** *exert* **only** an *antitussive effect*.

Non-opioids/Non-narcotic/Non-addicting Antitussives

Diphenhydramine

Promethazine

Chlorpheniramine

- ***First generation*** **antihistamines** (**cross BBB**; central mechanism) are *now can used as* **antitussives**.
- *Mechanism*; They *relieve* **cough** *due to their* **sedative** (*central*) and **anticholinergic actions**, *but* **lack** *selectivity* for **cough center**.
- **Diphenhydramine** [dye-fen-HYE-dra-meen], **Promethazine** [proe-METH-a-zeen] and **Chlorpheniramine** [klor-fen-IHR-ah-meen] are *commonly* **used**.
- *Many* **antihistamines** have been *added to* **antitussive/expectorant** *formulations*.
- **Diphenhydramine** *dose* in **cough** (*Pregnancy category* **B**);
  - *Adult*; **25 mg** *every* **4 hours.**
  - **2-6 years: 6.25 mg orally** *every* **4 hours.** - **6-12 years: 12.5 mg orally** *every* **4 hours.**

Butamirate (Sinecod®)

- **Butamirate** [BOO-ta-MY-rat] is a *central non-narcotic* **antitussive**.
- *Mechanism*; *depress* **cough center** *with moderate* **bronchodilator** *effect*.
- **Butamirate** *can be used even* in **infants** (Sinecod® *drops*).
- **Butamirate** **produce** *efficacy similar to* **Dextromethorphan** with *safe profile*.
- *Dose*; **7.5 mg/5mL**; - *Adult* **15 mL 4 times daily** - *Child*; **5 mL 3 times daily** (*Category*; **C**).

Cloperastine (Notussil®)

Levocloperastine

- **Cloperastine** [KLO-pee-RA-steen] is an **antitussive**, **antihistamine** and **anticholinergic agents**.
- **Levocloperastine** [lee-voe-KLO-pee-RA-steen] is the *levo isomer* of **Cloperastine**.

Dropropizine (Tussapine®)

Levodropropizine

- **Dropropizine** is [DRO-proo-PYR-az-een] is an **antitussive** and *central* **sedative agent**.
- **Levodropropizine** [lee-voe-DRO-proo-PYR-az-een] is the *levo isomer* of **Dropropizine**.

Clofedanol or Chlophedianol (Ulone®)

- **Clofedanol** [KlO-fe-DA-nol] is a *centrally acting* **cough suppressant**.
- **Clofedanol** has *local anesthetic* and *antihistamine* **properties**, and may have *anticholinergic effects* at **high doses**.

Clobutinol (Silomat®)

- **Clobutinol** [klo-BYOO-ty-nol] is a *centrally acting* **cough suppressant**.
- **Clobutinol** has the *potential* to *prolong* the **QT interval**, it was **voluntarily** *withdrawn* from *some* **countries (Germany).**

Oxeladin (Paxeladine®)

- **Oxeladin** [OX-e-LA-deen] is a ***highly potent*** and ***effective*** **antitussive drug** used to treat ***all types*** of **cough** *because* it ***helps to*** *clear* the **respiratory tract** *from excess* **secretions**.
- It may be ***used*** at **every age** (*available as* **drops, syrup** and **tablets**), ***as well as*** in ***patients with*** **heart disease**, since it has a ***high level*** of **safety** and a ***great selectivity to*** act on the **cough center**.

Carbetapentane or Pentoxyverine (Solotuss®) (Cabella®)

- **Carbetapentane** [kar-bay-ta-PEN-tane] is ***central*** **antitussive** by ***inhibition of*** **cough center**.
- It is available **alone** or in ***combination with*** **Guaifenesin** or with **Pseudoephedrine**.
- ***Adult dose***; **10-20 mg** ***every*** **4-6 hours**. - ***Pregnancy*** *category*; **N** (FDA has not classified the drug).
- ***Overdose*** leads to **anticholinergic** ***side effects***.

Pipazethate or Pipazetate (Selgon®)

- **Pipazethate** [pai-PA-zee-that] is a ***central and peripheral*** **antitussive** by ***inhibition of*** **cough center** and **peripheral neural** ***receptors*** in the **lung**.
- It has a ***bronchodilator effect*** which ***reduce spasm*** *during* **cough**.
- It may be ***used*** at **every age** (*available as* **drops, tablets** and **supp.**).
- ***Adult dose***; **20 mg orally** ***3 times daily***. - ***Pregnancy*** *category*; **N** (FDA has not classified the drug).

Benproperine (Pectipro®)

- **Benproperine** [ben-PRO-pe-REN] is ***central and peripheral*** **antitussive** by ***inhibition of*** **cough center** and **peripheral neural** ***receptors*** in the **lung**.
- It has a ***bronchodilator effect*** which ***reduce spasm*** *during* **cough**.
- **Other** ***central*** **antitussive agents** (*not widely used*); **Dibunate**, **Dimethoxanate**, **Fedrilate**, **Glaucine**, **Meprotixol**, **Morclofone**, **Caramiphen**, **Nepinalone**, **Oxolamine** and **Zipeprol**.

Peripheral Antitussives

Peripheral Cough Reflex Inhibitors

Benzonatate (Tessalon®)

- **Benzonatate** [ben-ZOE-na-tate] ***suppresses*** the **cough reflex** through ***peripheral*** **action**.
- **Benzonatate** is **chemically** ***related to*** the **ester-linked class** of **local anesthetic drugs**.
- It ***works by*** **anesthetizes** ***peripheral*** **neural receptors** (**stretch receptors**) in the **lung**.
- ***Adult dose***; **100-200 mg orally** ***3 times daily***. - ***Pregnancy*** *category*; **C**.
- **Inhaled Local Anesthetics** (**Lignocaine/Lidocaine**); has been shown to be able to ***suppress*** **cough** ***induced by*** *inhaled* **Capsaicin** in ***nonsmoking*** **volunteers**.
- *Excessive* **absorption** of **Benzonatate** in the **oral mucosa** will result in the ***rapid development*** of **numbness** of the **mouth** and **throat**.

Prenoxdiazine (Philobaxine®) (Libexin®)

- **Prenoxdiazine** [pree-NOX-dya-zeen] act by ***blocking*** **peripheral cough reflexes**.
- It also ***possesses*** **local anesthetic** and **bronchodilator** ***effect***.

Others

- **Honey**[##]; ***effective*** *for* ***relieving*** **cough**, and ***improving*** **sleep** in **children**. ***Dose***; **8.5 mg (½ tsp)** for ***ages*** **2-5 years**, **17 mg (1 tsp)** for ***ages*** **6-11 years**, and **34 mg (2 tsp)** for ***ages*** **12-18 years**, *administered as* a **single dose 30 minutes** ***before*** **bedtime**.

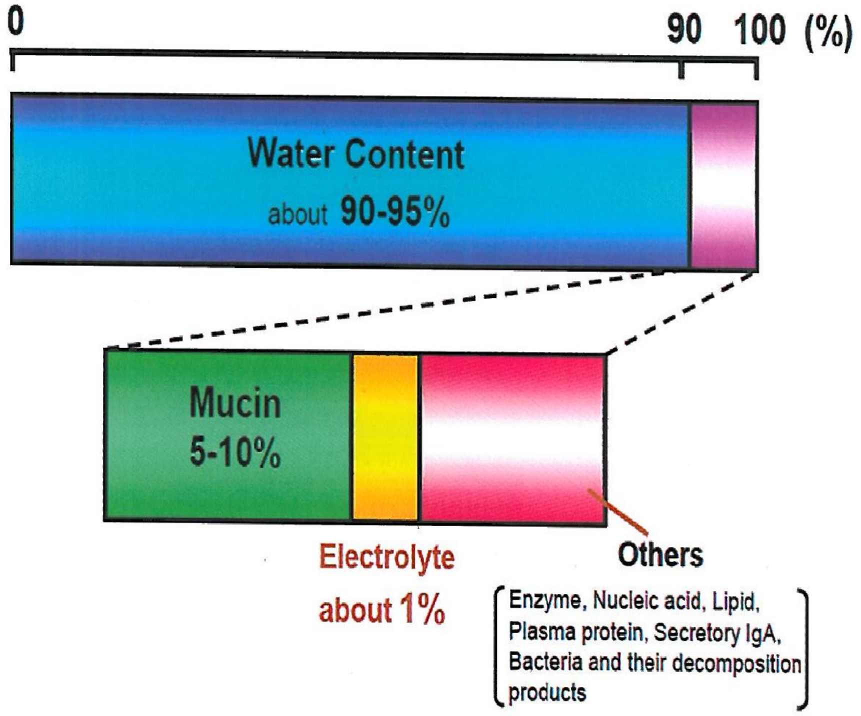
  Should not be used in **children < 1 year** *because* of possible ***contamination with*** *Clostridium botulinum*
- **Chest rub**; **Vicks® VaporRub®**[##]; is a ***topical*** **petrolatum-based gel** ***contains*** **Menthol**, **Eucalyptus oil** and **Camphor**, ***applied*** **once** to the **upper chest** and **neck** ***before*** **sleep** at a dose of **5 mL** for **children** ***ages*** **2-5 years** and **10 mL** for **children** ***ages*** **6-11 years**.
- **NSAIDs**; **Naproxen**[**] The ***only*** **NSAID** ***recommended*** in the **guidelines** for treatment of **cough** ***associated with*** **common cold** (because it was the only NSAID studied in this setting).
- ***Inhaled*** **Ipratropium**[**]; ***recommended in post-infectious*** **cough** or **chronic bronchitis**.
- **ICS**[**]; ***recommended in post-infectious*** **cough** if ***Inhaled*** **Ipratropium** is ***not effective***.
- **N.B.**; ***Central-acting*** **antitussives**[**]; are ***recommended in post-infectious*** **cough** if ***both*** ***Inhaled*** **Ipratropium** and **Inhaled Corticosteroids** (**ICS**) are ***ineffective***.

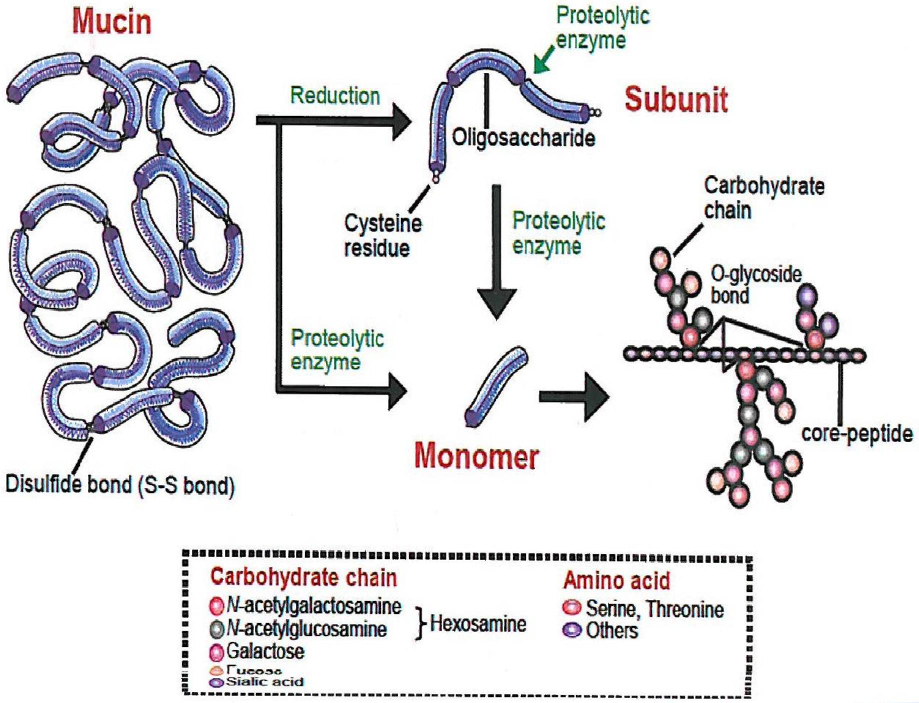
[**] 2006 American College of Chest Physicians (ACCP) Diagnosis and Management of Cough guidelines

[##] 2012 American Academy of Family Physicians (AAFP) Treatment of the Common Cold in Children and Adults

- **Steam inhalation**; **Tincture Benzoin** and **Menthol**.
- **Pharyngeal Demulcents**; ***soothing action*** on **irritating mucosa**.
- **Zinc** have been used in **OTC cold** and **cough drugs** but show ***no significant*** **improvement** of **cough**.
- **Antitussive Medicinal Herbs**; ***mechanisms of actions*** of **cough** are ***not always*** **known**. The medicinal herbs proved to possess antitussive property are *Abies webbiana, Adhatoda vasica, Althaea officinalis, Arctium lappa, Asparagus racemosus, Bergenia ciliata, Carum copticum, Cassia fistula, Crocus sativus, Cuminum cyminum, Drymaria cordata, Emblica officinalis, Glycyrrhiza glabra, Glycyrrhizae radix, Guiera senegalensis, Ionidium suffruticosam, Jussiaea suffruticosa, Leucas lavandulaefolia, Lagerstroemia parviflora, Mahonia aquifolium, Malva mauritiana, Nigella sativa, Paederia foetida, Passiflora incarnata, Prunus persica, Rudbeckia fulgida, Salvia officinalis, Stemona tuberose, Terminalia belerica, Trichodesma indicum, Vigna trilobata* and *Xanthium strumarium*.

➤ Mucus Structure:-


0
90
100 (%)
Water Content
about 90-95%
Mucin
5-10%
Electrolyte
about 1%
Others
Enzyme, Nucleic acid, Lipid, Plasma protein, Secretory IgA, Bacteria and their decomposition products


Mucin
Disulfide bond (S-S bond)
Reduction
Proteolytic enzyme
Proteolytic enzyme
Subunit
Oligosaccharide
Cysteine residue
Proteolytic enzyme
Monomer
Carbohydrate chain
O-glycoside bond
core-peptide
Carbohydrate chain
N-acetylgalactosamine
N-acetylglucosamine
Hexosamine
Galactose
Fucose
Sialic acid
Amino acid
Serine, Threonine
Others

➢ Mucoactive Drugs:-

Mucoactive Drugs	Potential Mechanism of Action
Mucolytics	**- Drugs that *decrease* mucus *viscosity*.**
N-AcetylCysteine (NAC)	- Breaks disulphide bonds linking mucin polymers. - Antioxidant and anti-inflammatory effects.
N-Acystelyn (Nacystelyn)	- Increases chloride secretion and breaks disulphide bonds.
Erdosteine	- Breaks disulphide bonds, modulates mucus production and increases mucociliary transport action.
Bromhexine	- Dissolves/breaks the mucus plug by depolymerize the mucopolysaccharide fibres as well as liberating lysosomal enzyme. - Induces copious watery mucus secretion (expectorant).
Dornase alfa	- Hydrolyses the DNA in mucus and reduces viscosity in the lungs.
Gelsolin	- Severs actin filament cross-links.
Thymosin β4	- Severs actin filament cross-links.
Dextran	- Breaks hydrogen bonds and increases secretion hydration.
Heparin	- Breaks both hydrogen and ionic bonds.
Mucoregulators	**- Drugs that *regulate* mucus *secretion*.**
Carbocysteine	- Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production.
Anticholinergics	- Decreases secretion volume.
Glucocorticoids	- Reduces airway inflammation and mucin secretion.
Macrolide Antibiotics	- Reduces airway inflammation and mucin secretion.
Mucokinetics	**- Drugs that *increase* muco-ciliary clearance by acting on the cilia.**
Ambroxol	- Stimulates surfactant production & inhibits neuronal sodium channels
Bronchodilators	- Improves cough clearance by increasing expiratory flow.
Surfactants	- Decreases sputum/mucus adhesiveness.
Expectorants	**- Drugs that *expulsion* of the mucus and *increase* the cough reflex**
Guaifenesin	- Stimulates secretion and reduces mucus viscosity.
Hypertonic Saline	- Increases secretion volume and/or hydration.

Mucolytics/Mucoregulators/Mucokinetics

N-AcetylCysteine (NAC)

- **N-Acetylcysteine** [N-a-SEET-il-SIS-teen] (**NAC**) is a **mucolytic** and **antidote** (**Paracetamol** toxicity) **drug**, with ***antioxidant*** and ***anti-inflammatory properties***.
- *Mechanism of action*;
    - *Decreases* **thickness** (**viscosity**) of **mucous secretions** in **lung**; by ***breaks*** **disulphide bonds** in ***mucoprotein*** (**mucin**) in **sputum**.
    - *Protects* **liver** by ***maintaining*** or ***restoring*** **glutathione** *levels*.
- *Uses*; - ***Adjuvant therapy*** for ***patients with*** **abnormal mucous secretions**; *such as* **emphysema**, **cystic fibrosis** and **chronic obstructive pulmonary disease** (**COPD**).
    - *Prevention* or *decreasing* of **liver damage** after **Paracetamol toxicity**.
- *Dose*; in ***abnormal*** **mucous** ***secretions***; - ***Pregnancy*** *category*; **B**.
    - ***Inhalation***; 1-2 mL of 10% solution may be given as often as every hour.
    - ***Direct instillation*** (into respiratory tract); 2-5 mL of the 20% solution.
    - ***Nebulization***; 3-5 mL of 20% solution or 6-10 mL of the 10% solution 3 to 4 times a day.

DON'T mix with antibiotics in the same nebulizer

- There are *several* **similar compounds** that **contain sulfhydryl groups** *such as*, **MethylCysteine** and **N-Acystelyn** (**lysine salt** *alternative to* **NAC**) that can ***effectively depolymerize*** **mucin polymers**.

Erdosteine (Mucotec®)

- **Erdosteine** [ER-doo-ST-een] is a **mucolytic** ***agent*** with ***antioxidant properties***.
- **Erdosteine** is ***prodrug*** *contains* **2** blocked **sulfhydryl (SH) groups** which are ***released following*** **first-pass metabolism**. The **3 active metabolites** ***exhibit*** **mucolytic** and ***antioxidant*** **activity**.
- *Mechanism of action*; ***Breaks*** **disulphide bonds**, ***modulates*** **mucus production** and ***increases*** **mucociliary transport** ***action***.
- *Dose*; **150-300 mg orally twice** ***daily***.

Bromhexine (Bisolvon®)

- **Bromhexine** [BRO-m-hek-seen] is a **mucolytic expectorant** ***agent*** with ***antioxidant properties***.
- *Mechanism of action*;
    - ***Decreases*** **viscosity** of **mucous secretions** in **lung**; by ***de-polymerization*** of **muco-polysaccharides** *as well as* ***liberating*** **lysosomal enzymes**.
    - ***Induces*** **copious watery mucus** ***secretion*** (*expectorant action*).
- *Dose*; **4-8 mg orally 3-4** ***times daily***. - *Pregnancy* ***category***; **A**.

Dornase-alfa (Pulmozyme®)

- **Dornase-alfa** [DOR-nase AL-fuh] is a ***recombinant*** **human deoxyribonuclease I (rhDNase)**, an ***enzyme*** which *selectively* ***cleaves*** **DNA present in sputum/mucus** of **cystic fibrosis** ***patients*** and ***reduces*** **viscosity** in the **lungs**, ***promoting*** **clearance** of ***secretions***.

CarboCysteine or Carbocisteine or CarboxyMethylCysteine (Mucosol®)

- **CarboCysteine** [KA-rbo-SIS-teen] (**Carbocisteine** or **CarboxyMethylCysteine**) is the ***most frequently*** **prescribed mucoactive agent** (**mucoregulator**) for ***long-term*** **COPD** ***use***.
- **CarboCysteine** has ***antioxidant*** and ***anti-inflammatory properties***.
- **Carbocisteine** is ***available as*** an ***oral formulation*** and *achieves* ***good*** **penetration** into **lung tissue** and **bronchial secretions**.
- *Mechanism of action*; ***Not act*** **directly** *upon the* **mucus structure**, in ***contrast to*** **NAC**.
    - ***Increase*** the **synthesis** of **sialomucins** (important structural components of mucus) → ***restoring*** the **viscoelastic properties** of **mucus**.
    - ***Increase*** **chloride** ***transport*** *across the* **airway epithelium**, which may *contribute towards* its **mucoregulatory** ***action***.
- *Dose*; **20 mg/kg orally** ***daily*** in *divided doses*. - *Pregnancy* ***category***; **C**.

Ambroxol (Mucosolvan®)

- **Ambroxol** [ah-M-bro-X-ul] is a **secretolytic** (**mucolytic**) and **secretomotoric drug** that ***restore*** the **physiological clearance** ***mechanisms*** of the **respiratory tract**.
- **Ambroxol** is a ***metabolite of*** **Bromhexine**.
- *Mechanism of action*; ***several mechanisms*** *including*;
    - ***Stimulates*** **mucociliary** ***transport rate*** by ***stimulates*** **synthesis** and **release** of **type II pneumocytes surfactant** (surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall and providing protection against infection and irritating agents).
    - ***Potent inhibitor*** of the **neuronal Na^+ channels** (this property led to the development as a lozenge to relief pain in acute sore throat).
- *Dose*;
    - *Adult*: **60-120 mg** ***daily*** in **2-3** ***divided doses***.
    - *Child*: **2-5 years**: **7.5 mg 3 times** ***daily***. - **6-12 years**: **15 mg** ***twice*** or **3 times** ***daily***.
- *Pregnancy*; ***avoid use*** *during* the **first trimester** of **pregnancy**.

Expectorants

- **Expectorants**; **Drugs** that ***expulsion*** of **mucus** ***from*** the **respiratory tract**. This ***typically*** **requires** a **coughing** ***action*** to ***loosen*** and **bring up** the **mucus** *from* the **respiratory tract**.
  - **Guaifenesin** (**glyceryl Guaiacolate**) is a ***centrally acting*** **muscle relaxant** that may also have an ***expectorant effect***. **Guaifenesin** is an ***expectorant drug*** **sold OTC**.
  - **Syrup of ipecac** (***Ipecacuanha***); is a ***powerful*** **emetic**, used in ***cough mixtures*** as an **expectorant** or an **emetic** from the 18th until the early 20th century.
  - **Hypertonic saline**; ***Aerosol inhalation*** of **Saline** or **Mannitol** has been ***previously*** *thought to* ***induce*** **ciliary motility**, **proteolysis** and **mucus liquefaction** by **osmosis**.
  - ***Aerosol inhalation*** of **Ammonium chloride/bicarbonate**, **Sodium/Potassium citrate** and **Potassium iodide**; ***promote*** the **secretion** of **airway fluids**. **Potassium iodide** ***should not*** be *administered to* **pregnant** or **hyperthyroid**.

Guaifenesin or Guaiphenesin or Glyceryl Guaiacolate

- **Guaifenesin** [gwye-FEN-e-sin] is an **expectorant drug** ***sold*** **OTC**.
- **Guaifenesin** has ***no*** **mucolytic** ***action*** but may ***reduce*** **bronchial sputum surface tension** and is *sometimes* ***combined with*** **antitussives**.
- ***Mechanism of action***;
  - ***Increasing*** **volume** and ***reducing*** **viscosity** of **bronchial secretions**.
  - ***Increasing*** **ciliary** ***movement*** and ***increase*** the **efficiency** of the **cough reflex** → ***facilitate*** **removal** of **secretions**.
- **Guaifenesin** has **muscle relaxant** and **anticonvulsant** ***properties increases*** the **analgesic effect** of **Paracetamol** and **Aspirin**, *increases* **sedative effects** of **alcohol**, **tranquilizers** and **anesthetics**.
- ***Adult dose***; - *Immediate release*; **200-400 mg orally** ***every*** **4 hours**. - ***Pregnancy category***; **C**.
  - *Sustained release*; **600-1200 mg orally** ***every*** **12 hours**.
- **Guaifenesin** (**expectorant**) + **Oxomemazine** (***sedative*** **antihistamine**); Toplexil$^{®}$.

➢ Drugs recommended in the new (2006) American College of Chest Physicians (ACCP) guidelines for the treatment of acute and sub-acute cough:-

Agent or class of agents	Cough associated with common cold	Acute bronchitis	Postinfectious Cough	Pertussis (whooping cough)
Central-acting Antitussives	Not recommended	Recommended	Recommended if both inhaled ipratropium & inhaled corticosteroids are ineffective	Not recommended
First-generation Antihistamine/ Decongestants	Recommended	Not recommended	Not recommended	Not recommended
Inhaled **Ipratropium**	Recommended	Not recommended	First-line therapy	Not recommended
Naproxen	Recommended	Not recommended	Not recommended	Not recommended
Inhaled **Corticosteroids**	Not recommended	Not recommended	Recommended if inhaled ipratropium is not effective	Not recommended
β_2-Agonist bronchodilators	Not recommended	Recommended only when wheezing accompanies the cough	Not recommended	Not recommended
Antibiotics	Not recommended	Not recommended	Recommended only if associated with bacterial sinusitis	Macrolide antibiotics recommended early in the course of infection (first few weeks)

Allergic Rhinitis (AR)

➢ Overview:-

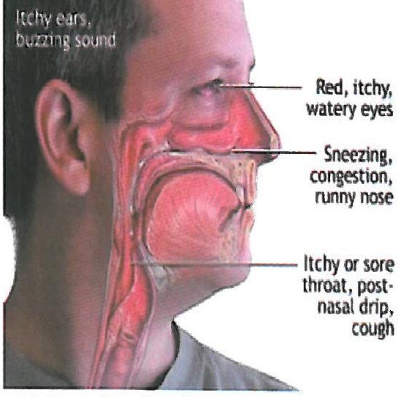
- **Allergic rhinitis** (**rhinitis** or **hay fever**) is a ***type of*** **inflammation** of the **nasal membranes** *occurs when* the **immune system *interact*** with an **allergens** in the **air**.
- It is ***characterized by*** **sneezing**, **nasal congestion**, **nasal itching**, and **rhinorrhea**, in ***any*** **combination**.
- An **attack** may be ***precipitated by inhalation of*** an **allergen** (such as **dust**, **pollen**, or **animal dander**).
- The **fluid** *from the* **nose** is ***usually*** **clear**.
- **Symptom *onset*** is often *within* **minutes** *following* **exposure**.
- The **foreign material** (**allergens**) ***interacts with*** **mast cells** *coated with* **IgE *generated*** in ***response to*** a *previous* **allergen exposure**.
- The **mast cells *release*** **mediators**, *such as* **histamine**, **leukotrienes** and **chemotactic factors**.
- The ***prevalence*** of **allergic rhinitis** in the **United States** *ranges from* **3-19%**, and **30** to **60 million people** are ***affected*** **each year**.
- **Antihistamines** and/or ***intranasal*** **corticosteroids** are ***preferred therapies***.

➢ Definition:-

- **Allergic rhinitis** (**AR**); is an ***inflammatory***, **IgE-*mediated*** **disease** *characterized by* **nasal congestion**, **rhinorrhea** (nasal drainage), **sneezing** and/or **nasal itching**.

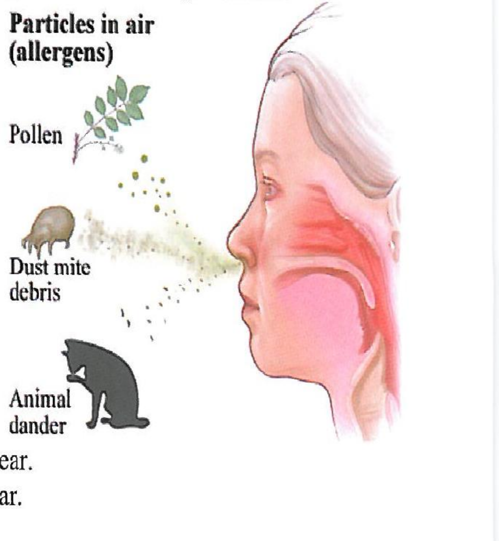
➢ Signs and symptoms:-

- **Rhinorrhea*** (excess nasal secretion)
- **Nasal congestion***
- **Itching***; nose, eyes, ears, palate
- **Sneezing***
- **Eye redness** and **swelling**
- **Postnasal drip** (nasal secretion accumulates in throat)
- **Anosmia**
- **Headache**
- **Earache**
- **Fatigue** and **drowsiness**


Itchy ears, buzzing sound
Red, itchy, watery eyes
Sneezing, congestion, runny nose
Itchy or sore throat, post-nasal drip, cough

➢ Classifications: *New classification*; 2015 AAO-HNSF guidelines for allergic rhinitis;

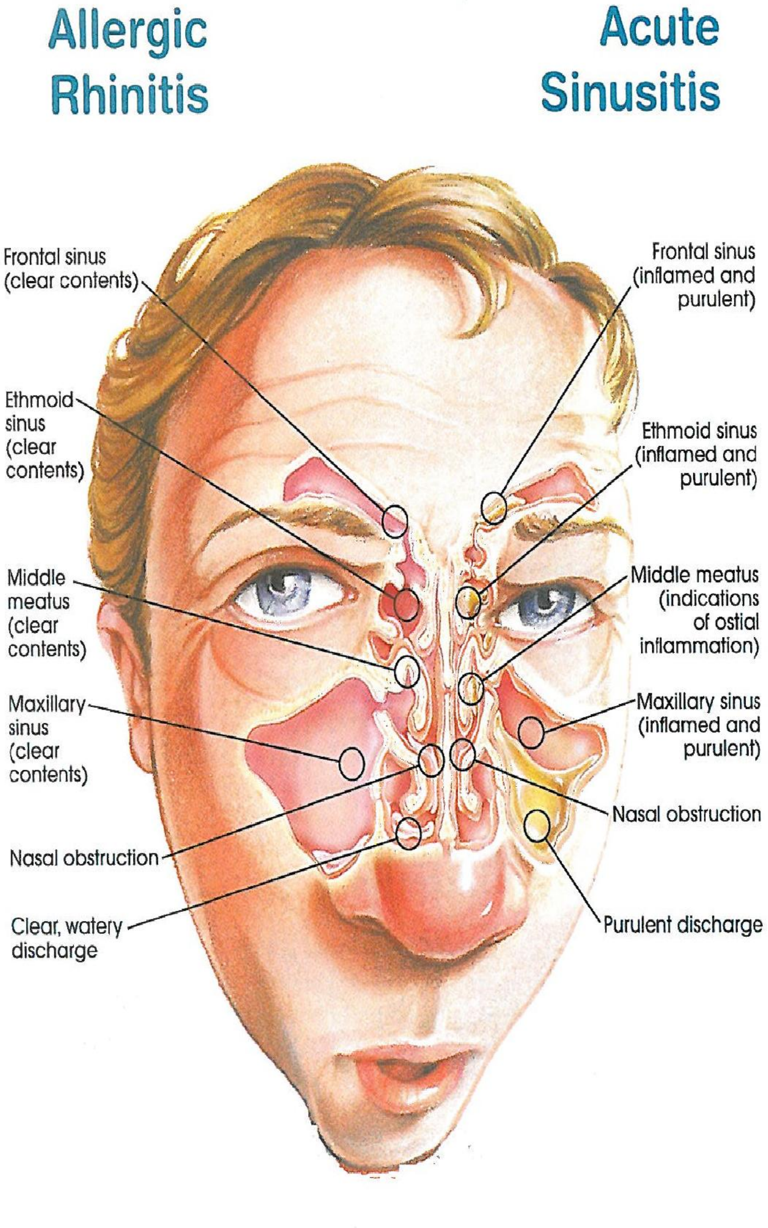
- *According to* **temporal pattern of exposure**;
  1) **Seasonal** [**hay fever**] (***seasonal-related***);
     - ***Trigger***; **Pollen**; tree, grass, and weed.
     - *Usually* in ***late*** **summer** or **spring**.
     - *Usually* **develop *after*** **6 years of age**.
  2) **Perennial** (***year round***);
     - **Occurs** *throughout the* **year**.
     - ***Trigger***; **House dust mites**
  3) **Episodic**;
     - ***Trigger***; ***not normally*** **present** in the **patient's environment**, e.g., ***visiting*** a **home** *with* **pets** (**animal dander**).



- *According to* **frequency of symptoms**;
  1) **Intermittent**; <4 days/week or <4 weeks/year.
  2) **Persistent**; >4 days/week and >4 weeks/year.
- *According to* **severity of symptoms**;
  1) **Mild**; *when* **symptoms** are ***present*** but are ***not interfering*** with **quality of life**
  2) **More severe**; *when* **symptoms** are **bad enough** to ***interfere*** with **quality of life**.

➢ Non-allergic Rhinitis:-

- The ***symptoms*** of **non-allergic rhinitis** are ***similar to*** those of **allergic rhinitis**, but ***none*** of the ***usual evidence*** of an **allergic reaction** is ***present***.
  - **Infectious rhinitis** (**Sinusitis** or **Rhinosinusitis**; see infectious diseases in chemotherapy chapter);
    - A) **Acute sinusitis** (***last** up to* **4 weeks**); *usually* **viral infection** (common cold or influenza); lasts up to 10 days and that completely resolves in 99% of cases.
    - B) **Chronic sinusitis** (***last** up to* **12 weeks**); **bacterial infection**.
  - **Occupational** or **environmental rhinitis**; secondhand smoke or strong odors.
  - **Gustatory rhinitis**; hot or spicy foods and alcoholic beverages.
  - **Drug-induced rhinitis**; **Antihypertensive** (**β-blockers**, **α-blockers** and **ACEIs**), **NSAIDs**, **Oral contraceptives**, ***medications for*** **erectile dysfunction** (**Sildenafil**) and **rhinitis medicamentosa**; **RM** (***rebound rhinitis;*** overuse of decongestant nasal sprays).
  - **Hormonal rhinitis**; **Hypothyroidism**, **menstrual cycle**, **oral contraceptives** & **pregnancy**.
  - **Vasomotor rhinitis**; **Weather** or **emotional *changes*** and **exercise**.
  - **Non-allergic rhinitis with eosinophilia syndrome** (**NARES**); presents as congestion and nasal eosinophilia with no obvious allergic source detected on skin testing.


Allergic Rhinitis
Acute Sinusitis
Frontal sinus (clear contents)
Ethmoid sinus (clear contents)
Middle meatus (clear contents)
Maxillary sinus (clear contents)
Nasal obstruction
Clear, watery discharge
Frontal sinus (inflamed and purulent)
Ethmoid sinus (inflamed and purulent)
Middle meatus (indications of ostial inflammation)
Maxillary sinus (inflamed and purulent)
Nasal obstruction
Purulent discharge

➢ Diagnosis:-

- **Patient history** and **physical examination**;
  - *Patient presents* with **one** or **more** *of the following* **allergic symptoms**;
    - **Nasal congestion, rhinorrhea, itching, sneezing**, or **red** and **watery eyes**.
- **Allergy testing**;
  - **Immunoglobulin E–specific** ***skin*** **or** ***blood*** **testing** is ***recommended*** *when* **has been ineffective**, a ***diagnosis*** of **allergic rhinitis** is ***uncertain***, or ***when*** **knowledge** of the ***specific*** **causative allergen** is *needed to* **target therapy**.
- **Imaging**;
  - ***Should not*** *routinely* ***perform*** **sino-nasal imaging** in **patients** ***presenting*** with **symptoms** ***consistent with*** a *diagnosis of* **allergic rhinitis**.
- **Chronic diseases** and **comorbidities**;
  - ***Should*** **assess patients** with a ***clinical diagnosis*** of **allergic rhinitis** in the ***presence of*** **associated conditions** *such as* **asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis** (**sinusitis**), and **otitis media**.

➢ Managements:-

A) **Environmental Control**;

- **Allergen** ***avoidance*** *measures* may ***improve*** **health outcomes** for ***patients with*** **allergic rhinitis**, such as ***removing*** **pets** *from* **home**, the use of **air filtration** ***systems***, **bed covers**, and **acaricides** (***chemical agent*** that ***kills*** **dust mites**).

Although dust mite allergies are common, studies have not found any benefit to using mite-proof impermeable mattresses or pillow covers (evidence rating; grade A)

B) **Pharmacological Management**;

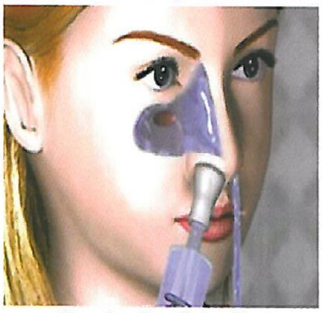
1) *Intranasal* **Corticosteroids** (***strong recommendation***); **1st line**; Moderate-Severe
2) *Oral* **Antihistamines** (***strong recommendation***); **1st line**; Mild-Moderate
3) *Oral* **Leukotriene Receptor Antagonists** (***recommendation***); Coexistent asthma
4) *Intranasal* **Antihistamines** (***option***); If symptoms not improved with oral antihistamines
5) **Decongestants** (***option***); Short term-use if congestion not improved with INCs
6) *Intranasal* **Mast-Cell Stabilizer** (***option***); Before exposure to specific known allergy
7) *Intranasal* **Anticholinergics** (***option***); For sever persistent rhinorrhea
8) *Combination* **Therapy** (***option***); If inadequate response with monotherapy

C) **Immunotherapy**; ***recommended*** for ***moderate*** or ***severe persistent*** **allergic rhinitis** ***not responsive*** to ***usual*** **treatments**.

1) ***Sublingual*** **Grastek**
2) ***Sublingual*** **Oralair**
3) ***Sublingual*** **Ragwitek**
4) ***Subcutaneous*** **allergen extracts**

D) **Others**;

1) **Inferior Turbinate Reduction** (***option***)
2) **Acupuncture** (***option***)
3) **Herbal Therapy** (***No recommendation***)



Nasal saline ***irrigation***

Pharmacologic Therapy

- ***Recommendations***;

* **Nasal saline** ***irrigation*** is ***beneficial*** in ***treating*** the **symptoms** (***not*** **treatment**) of **allergic rhinitis** and may be ***used*** **alone** or as **adjuvant therapy**.

* **Intranasal Corticosteroids** and **Oral Antihistamines** are ***recommended as*** **first lines** of **treatment**.

* **Intranasal Corticosteroids** ***alone*** *should be* the ***initial treatment*** for **allergic rhinitis** with **symptoms** ***affecting*** **quality of life**.

* **Second** and **Third-generation Antihistamines** have a ***better*** **adverse effect profile** and *cause* ***less*** **sedation** ***than*** **First-generation** with the ***exception*** of **Cetirizine** (Zyrtec®) [cause sedation].

* **Intranasal Antihistamines** ***not recommended*** as **first-line therapy** for **allergic rhinitis** ***because*** are ***more expensive***, ***less effective*** & have ***more adverse effects*** *than* **Intranasal Corticosteroids**.

1) *Intranasal* Corticosteroids (INCs)

First Generation

Beclomethasone (Becol®)	**Triamcinolone** (Nasacort® AQ)
Flunisolide (Nasarel®)	**Budesonide** (Rhinocort® Aqua)

Second Generation

Fluticasone Furoate (Avamys®)	**Fluticasone Propionate** (Flonase®)
Mometasone (Nasonex®)	**Ciclesonide** (Omnaris®)
Betamethasone (Betnesol®)	

- ***First generation*** **intranasal corticosteroids** are ***more*** **bioavailable** and tend to *produce* ***more*** **systemic adverse effects** than ***second generation*** **intranasal corticosteroids** are *less* **bioavailable** and have ***limited*** **systemic adverse effects.**
- *Mechanism*; act by ***decreasing*** the ***influx of*** **inflammatory cells** and ***inhibiting*** the ***release of*** **cytokines**, thereby ***reducing*** **inflammation** of the **nasal mucosa.**
- *Onset of action*; ***within*** **12 hours.** *Maximum Effectiveness*; **2-4 weeks** *of use.*
- *Indications*; *All* **9 intranasal corticosteroids** are ***approved by*** **FDA** ***for*** the ***treatment of*** **perennial and seasonal allergic rhinitis.**
- *Age*; - **FDA-Approved** ***for*** **≥ 2 years** *of* **age**; **Triamcinolone**, **Mometasone** and **Fluticasone Furoate.**
  - **FDA-Approved** ***for*** **≥ 4 years** *of* **age**; **Fluticasone Propionate.**
  - **FDA-Approved** ***for*** **≥ 6 years** *of* **age**; **Beclomethasone**, **Budesonide**, **Ciclesonide**, and **Flunisolide.**
  - **FDA-Approved** ***for*** **≥ 12 years** *of* **age**; **Beclomethasone dry nasal aerosol** (Qnasl®); is the first non-aqueous nasal formulation available (2012 FDA approved).
- *Recommendations*;
  - **INCs** are the ***drugs of choice*** for *treatment of* ***moderate*** to ***severe*** **allergic rhinitis.**
  - **INCs** are ***strongly recommended*** for **patients** whose ***symptoms interfere*** with their **quality of life.**
  - ***All of these*** **agents** ***reduce***; 1) **sneezing** 2) **itching** 3) **rhinorrhea** 4) **congestion.**
  - **INCs** are ***more effective*** *than* **oral** and **intranasal antihistamines** in the ***treatment of persistent*** or ***more severe*** **allergic rhinitis.**
- *Pregnancy*; *only* **Budesonide** has an **FDA pregnancy** ***category*** **B** and ***others*** are ***category*** **C.**
- *Local side effects*; **throat irritation, epistaxis, stinging, burning** and **nasal dryness.**
- *Systemic side effects*; ***No*** or ***limited*** **effects** on **Hypothalamic-pituitary-adrenal (HPA)** ***axis suppression*** and ***decreased*** **vertical growth of children** [***all*** **intranasal corticosteroids** ***carry*** **a warning** that ***long-term use*** may ***restrict*** **growth in children**].

2) *Oral* Antihistamines

Second Generation

Cetirizine (Zyrtec®)	**Loratadine** (Claritin®)	**Acrivastine** (Semprex®)
Ebastine (Kestine®)	**Mizolastine** (Zolim®)	

Third Generation

Levocetirizine (Allear®)	**Desloratadine** (Aerius®)	**Fexofenadine** (Telfast®)

- **Histamine** is the ***most mediator*** in ***early*** **allergic response**; causes **smooth muscle** ***constriction***, **mucus** ***secretion***, **vascular** ***permeability***, and **sensory nerve** ***stimulation***, resulting in the ***symptoms*** of **allergic rhinitis.**
- *First-generation* **antihistamines** (***high*** **lipid solubility** and ***more readily*** *cross* the **blood-brain barrier**) such as **Brompheniramine**, **Chlorpheniramine**, **Clemastine** and **Diphenhydramine**; ***may cause*** **sedation, fatigue** and ***impaired*** **mental status.** The ***use of*** **first-generation** ***sedating*** **antihistamines** has been *associated with* ***poor*** **school performance**, ***impaired*** **driving**, and ***increased*** **automobile collisions** and **work injuries.**
- ***Second*** and ***third-generation*** **antihistamines** (***more complex*** **chemical structures**, ***less*** **lipid solubility** and ***less*** **cross** the **blood-brain barrier**) have a ***better*** **adverse effect** ***profile*** and *cause* ***less*** **sedation**, with the ***exception of*** **Cetirizine** (Zyrtec®) [***partially*** **sedating**].
- *Onset of action*; **15** *to* **30** ***minutes.*** - **Oral Antihistamines**; ***safe*** **for children ≥ 2 years.**

- *Pregnancy*; **Cetirizine** and **Loratadine** are **FDA pregnancy** *category* **B**, while **Desloratadine** and **Fexofenadine** are *category* **C**.
- *Recommendations*;
    - Oral Antihistamines are the *drugs of choice* for *treatment of mild* to *moderate* allergic rhinitis.
    - Oral Antihistamines are *strongly recommended* for **patients** with **allergic rhinitis** and *primary complaints* of **sneezing** and **itching**.
    - Oral Antihistamines *reduce*; 1) sneezing 2) itching 3) rhinorrhea; *less effective* than INCs at *treating* nasal congestion and ocular symptoms.

3) *Oral* Leukotriene Receptor Antagonists

Montelukast (Singulair®)

- **Montelukast** is the ***only*** **leukotriene receptor antagonist** ***FDA-approved*** for use in ***seasonal*** and ***perennial*** **allergic rhinitis.**
- Montelukast; can be *used* in *children* < 2 years for **allergic rhinitis** and may be ***most beneficial*** in patients who also have **asthma.**
- *Pregnancy*; **Montelukast** has an **FDA pregnancy** *category* **B**.
- *Recommendations*;
    - Montelukast has a ***modest*** **effect** in *relieving* 1) sneezing 2) itching 3) rhinorrhea 4) congestion, but it is ***less effective*** than **intranasal corticosteroids.**
    - Montelukast is ***comparable to*** oral antihistamines but ***more expensive*** and ***should not*** be used as a ***first-line*** **treatment** of **allergic rhinitis.**
    - *Combination* of a Montelukast and *second/third-generation* antihistamines is ***superior to*** *either* **use** ***alone.***
    - Montelukast may be ***particularly*** **useful** in ***patients*** *with* ***coexistent*** **asthma** because it ***reduces*** **bronchospasm** and ***attenuates*** the **inflammatory** ***response.***

4) *Intranasal* Antihistamines

Azelastine (Astelin®)

- *Intranasal* antihistamines are an *option* for **patients** ***with seasonal, perennial*** and ***episodic*** **allergic rhinitis.**
- *Benefits*; is **targeted delivery** and *increased* **dosage** to **nasal tissues.**
- *Efficacy*; *similar* or *superior* to **oral antihistamines** for **nasal** *symptoms* & *may improve* **congestion.**
- Children; may use for children ≥ 5 years.
- *Pregnancy*; **Azelastine** has an **FDA pregnancy** *category* **C**.
- *Recommendations*; Intranasal antihistamines are an *option* if **symptoms** ***do not*** **improve** *with* **oral** ***second/third-generation*** **antihistamines**; because; Azelastine *twice* **daily dosing**, ***more expensive***, and ***decreased*** **effectiveness** ***compared with*** **intranasal corticosteroids.**
- *Local side effects*; **bitter taste, epistaxis, headache, somnolence** and **nasal** ***burning.***

5) Decongestants (*Oral/Topical*)

Pseudoephedrine	Phenylephrine
Oxymetazoline (Afrin®)	Xylometazoline (Otrivin®)

- **Oral** and **intranasal decongestants** ***improve*** **nasal congestion** ***associated with*** **allergic rhinitis** by ***acting on*** **α1-adrenergic receptors,** which causes *vasoconstriction* in the **nasal mucosa.**
- The ***most common*** **decongestants** are **Pseudoephedrine, Phenylephrine** and **Oxymetazoline.**
- *Common side effects* of **intranasal decongestants**; **sneezing** and **nasal dryness.**
- *Duration of therapy*; *not more* than **3-5 days**; *because* may *develop* **Rhinitis Medicamentosa (RM),** or **rebound rhinitis** or **recurring congestion.**
- *Patient Counselling*; **Patients** *using* **topical decongestants** *should understand* that if the **agents** are **used** *longer than* **3** days; *rebound* **congestion** [**Rhinitis Medicamentosa (RM)**] *will* **develop.**
- **Oral decongestants**; *may cause* **headache,** *elevated* **blood pressure** and **intraocular pressure, tremor, urinary retention, dizziness, tachycardia** and **insomnia.**
- **Pseudoephedrine** *should be* **used** *cautiously* in **patients** *with* **cardiovascular disease, hypertension, diabetes, hyperthyroidism, closed-angle glaucoma** or **bladder neck obstruction.**
- *Recommendations*; **Decongestants** may be ***considered for*** **short-term use** in ***patients without*** **improvement** in **congestion** with **intranasal corticosteroids.**

6) *Intranasal* Mast-Cell Stabilizer

Cromolyn (Nasalcrom®)

- **Mast cell stabilizers** ***decrease*** **inflammation** *associated with* **allergies** by ***inhibiting*** the **mast cell** ***release*** of **histamine** & ***other*** **inflammatory mediators**. It is ***given*** **30 min**. ***before*** **allergen** ***exposure***
- **Cromolyn** may be ***particularly*** **useful** ***for patients with*** a ***specific*** **known allergy** who **plan** on ***coming in*** *contact with* that **allergen**.
- **Cromolyn**; ***safe*** **for children ≥ 2 years**. - ***Pregnancy***; **FDA pregnancy** ***category*** **B**.
- ***Recommendations***; **Cromolyn** ***not considered*** **first-line therapy for allergic rhinitis** *because* it is ***less*** **effective** than **antihistamines** and ***intranasal*** **corticosteroids** and is ***given*** **3** or **4 times** ***daily***.

7) *Intranasal* Anticholinergics

Ipratropium (Atrovent®)

- **Ipratropium** has ***anti-secretory properties***, and when ***applied*** **locally**, ***inhibits*** **secretions** from **glands** *lining* the **nasal mucosa**.
- ***Intranasal*** **ipratropium** can used for ***treatment*** of ***severe*** **rhinorrhea** ***associated with*** **allergic rhinitis** ***not controlled*** by ***other*** **medications**.
- It ***does not relieve*** **sneezing, itching** or **nasal congestion**.
- **Ipratropium** ***may cause*** **dry nose** and **mouth, pharyngeal irritation**.

8) Combination Therapy

- ***Combination*** **therapy** is an ***option*** for **patients** ***with severe*** or ***persistent*** **allergic rhinitis** who have ***inadequate*** **response** to **monotherapy**.
- ***Recommendations***;
  - **Oral Antihistamines** and **Intranasal Corticosteroids**; If ***incomplete*** **control** or ***no*** **response** to ***intranasal*** **corticosteroids**, the ***addition of*** **oral antihistamines** is **ineffective**.
  - **Oral Antihistamines** and **Leukotriene Receptor Antagonists**. There is ***conflicting*** **evidence** that this ***combination*** is ***superior*** to ***either*** **medication** used ***alone*** and is ***not recommended***.
  - **Oral Antihistamines** and **Oral Decongestants**; This combination ***controls*** **allergic rhinitis** ***symptoms better than*** **oral antihistamines** or **oral decongestants** ***alone***, but ***increases*** **adverse effects** and there is a ***potential for*** **tolerance** from **long-term use**.
  - **Intranasal Corticosteroids** and **Leukotriene Receptor Antagonists**; **Leukotriene receptor antagonists** ***should not*** **be used routinely** as ***additive therapy*** **for patients** ***using intranasal*** **corticosteroids**.
  - **Intranasal Corticosteroids** and **Intranasal Antihistamines** (**Fluticasone/Azelastine** ***intranasal***; Dymista®) This ***combination*** is ***most effective*** **for patients** who ***tolerate*** either ***intranasal*** **corticosteroids** or ***intranasal*** **antihistamine** ***monotherapy***.
  - **Intranasal Corticosteroids** and **Intranasal Oxymetazoline**; This ***combination*** **controls allergic symptoms** ***more effectively than either*** **therapy** ***alone***. To ***avoid risk of*** **rhinitis medicamentosa**, use ***should be*** **limited to** ***fewer than*** **3 days**.

Immunotherapy

- **Immunotherapy should be** ***considered for moderate*** or ***severe persistent*** **allergic rhinitis** that is ***not responsive*** to **usual treatments** (***monotherapy*** or ***combination***).
- **Immunotherapy** is the ***only*** **treatment** that ***changes*** the ***natural course*** of **allergic rhinitis**, ***consists*** of ***administering*** a ***small amount*** of **allergen extract subcutaneously** or **sublingually**.
- **Omalizumab** (Xolair®), an ***anti-immunoglobulin E*** **antibody** ***approved for*** **asthma**, has been ***shown*** to be ***effective*** in ***reducing*** **nasal symptoms** and ***improving*** **quality of life** ***scores*** in ***patients with*** **allergic rhinitis**. The ***main*** **limitations** of its use are **high cost**.

Others

- **Inferior Turbinate Reduction**; ***Surgical options*** are *available for* **patients** who have ***persistent*** **nasal symptoms** and **turbinate hypertrophy** *despite* **medical treatment**.
- **Acupuncture**; for **patients** ***interested in*** **non-pharmacologic therapies, physicians** may ***suggest***.
- **Herbal Therapy**; ***no recommendation*** for ***using*** **herbal therapy** for ***patients with*** **allergic rhinitis**.

R; 2015 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guidelines for allergic rhinitis